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(54) Title: T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME

(57) Abstract

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.

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T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME

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TECHNICAL FIELD OF THE INVENTION

The present invention relates to cloned T-type calcium channels.

BACKGROUND OF THE INVENTION

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Biological membranes are themselves generally impermeable to ionic species. Thus, ions enter cells through regulated pores formed from membrane-associated proteins. Most of these regulated pores are voltage-dependent and are thus able to transduce changes in the transmembrane potential into ion flux. Voltage-gated ion channels form a "superfamily" of related proteins (cf. Jan et al., *Nature*, 345, 672 (1990)). Peculiar to this genus is a high degree of conservation in molecular structure. Generally, voltage-gated channels are membrane bound glycolsylated proteins formed of many subunits. Large α subunits form a pore in the membrane that is selective for a given ionic species. Each α subunit contains four domains (I, II, III, and IV). Each channel domain has six putative transmembrane helical segments (S₁-S₆). In general, the segments within each domain are similar but not identical. Aside from overall structural conservation, certain charged residues within the domains are highly conserved among voltage-gated ion channels (Jan et al., *supra*; Stühmer et al., *Nature*, 339, 597-603 (1989)).

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Differences in charged residues between groups of voltage-gated ion channels confer properties unique to each subgroup, such as ion selectivity. For example, most voltage gated ion channels are selective for either sodium, potassium or calcium. Known calcium channels require a ring of negative charge provided by glutamate residues found at similar locations in each of the domains (Yang et al., *Nature*, 366, 158-61 (1993)).

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Voltage-gated channels are often classified on the basis of their electrophysiology. The resting membrane potential of most animal cells is between about -70 mV and -80 mV. When the membrane becomes depolarized (moved towards 0 mV), various membrane channels become activated (they are said to

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"open"). Thus, one basis for classifying membrane channels is the membrane potential necessary to activate (or "gate") them (voltage dependency). For example, "T-type" calcium channels are activated at a lower voltage than L- or N-type channels (Nowycky et al., *Nature*, 316, 440-43 (1985)). Other physiological properties are the activation kinetics, inactivation kinetics, tail current (deactivation kinetics), and single channel conductance. Thus, in comparison to other calcium currents, T-type calcium current is characteristically short (Chen et al., *J. Gen. Physiol.*, 96, 603-30 (1990)), and it exhibits characteristically slow activation kinetics near threshold, fast inactivation kinetics, and slow tail current (Randall et al., *Neuropharmacol.*, 63, 879-93 (1997); Carbone et al., *Nature*, 310, 501-02 (1984); Nilius et al., *Nature*, 316, 443-46 (1985)).

Calcium currents have been implicated in many neurological and muscular functions. For example, T-type calcium current is associated with cardiac pacemaker activity, pain transmission in the central nervous system, and in other physiological functions. Defects in T-type calcium current have been implicated in cardiac arrhythmia, hypertension, and epilepsy. Given their potential clinical value, the pharmacological properties of calcium channels have been the subject of extensive study. Most such studies have involved L-type channels because, unlike T-type channels, L-type calcium channels are readily purified from cell extracts. For example, L-type calcium channels have been purified using dihydropyridine drugs (e.g., nifedipine) which can bind with sufficiently high affinity to serve as a ligand for purifying L-type calcium channels. Such purified and cloned L-type calcium channels have been used to develop assays for drugs affecting L-type calcium channels (see, e.g., U.S. Patents 5,429,921 and 5,386,025).

While many electrophysiological characteristics of T-type calcium currents are known, the lack of isolated T-type channels has stalled research into the pharmacology and biophysics underlying the T-type calcium current, at least in comparison with other calcium channels. Indeed, while it is generally assumed that voltage-sensitive ion channels are responsible for the current, no such channel protein, nor any nucleic acid encoding such a protein, has been isolated. In view of the foregoing problems, there exists a need for an isolated T-type calcium channel and a nucleic acid encoding a T-type calcium channel.

BRIEF SUMMARY OF THE INVENTION

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or

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substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.

The present invention is useful for exploring the electrophysiology and pharmacology of the T-type calcium current. Such knowledge can lead to the development of drugs for potentiating or attenuating T-type calcium channels. Thus, the present invention provides an assay for identifying potential drugs affecting T-type calcium channels by exposing cells expressing a T-type calcium channel to a putative drug and then measuring the calcium flux in response to a change in membrane potential. The identification of drugs affecting T-type calcium channels will facilitate even greater understanding of the biophysics of these proteins. Furthermore, some such drugs could have potential clinical applications.

The invention can best be understood with reference to the accompanying drawings and in the following detailed description of the preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1E compare the complete amino acid sequences of three types of T-type calcium channels (α 1G (or Ca,T.1), α 1H (or Ca,T.2), and α 1I (or Ca,T.3)), indicating conserved functional domains.

Figures 2A-2D are graphic representations of the current-voltage relationships of three cloned T-type calcium channels (Figures 2A, 2B, and 2C) and a cloned R-type calcium channel (Figure 2D).

Figure 3A is a graphic representation of the average current-voltage curve for cloned T-type calcium channels (α 1G, triangles, α 1H, inverted triangles, α 1I, circles), and a cloned R-type calcium channel (filled squares). Figure 3B compares the normalized conductance of a cloned T-type calcium channel at three different concentrations of BaCl₂.

Figure 4 depicts average kinetics of the tail current as a function of repolarization potential for $\alpha 1G$ (triangles), $\alpha 1H$ (inverted triangles), $\alpha 1I$ (circles), and a cloned R-type calcium channel (filled squares).

Figures 5A and 5B graphically present data concerning the use of a cloned T-type calcium channel to detect drugs affecting the channel. Figure 6A depicts the effect of 100 μ M on current-voltage relationships with a single dosage of miberfradil. Figure 6B illustrates the effect on T-type channel conductance of various doses of miberfradil.

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DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel α

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subunit. The nucleic acid can be of any type, and it can include other elements aside from a sequence encoding a T-type calcium channel domain or domains. For example, where the nucleic acid comprises RNA, it can also include regulatory sequences suitable to permit translation of the RNA. Thus, an RNA nucleic acid of the present invention preferably has at least one ribosome entry site, and preferably has a polyadenosine tail for stabilizing the RNA in the cellular environment. Similarly, DNA nucleic acids of the present invention can have regulatory elements for promoting the transcription of sequence encoding the T-type calcium channel into an RNA such as that described above. For example, a DNA nucleic acid of the present invention can have a promoter and/or an enhancer sequence. While the nucleic acid can be any type of nucleic acid, the nucleic acid preferably comprises a cDNA. A cDNA nucleic acid is preferred over other nucleic acids to permit the nucleic acid to be readily cloned, sequenced, and expressed in a wide variety of cells.

The choice of promoter and/or an enhancer will largely depend on the milieu in which the nucleic acid is to be expressed. Thus, for expression in bacterial cells, the regulatory elements are bacterial promoters. Similarly, for expression in mammalian cells, the regulatory elements are able to effect expression in mammalian cells. While many such regulatory elements are known in the art, examples include prokaryotic promoters and viral promoters (e.g., retroviral ITRs, LTRs, immediate early viral promoters (IEp), such as herpesvirus IEp (e.g., ICP4-IEp and ICP0-IEp), cytomegalovirus (CMV) IEp, and other viral promoters, such as Rous Sarcoma Virus (RSV) promoters, and Murine Leukemia Virus (MLV) promoters). Other suitable promoters are eukaryotic promoters, such as enhancers (e.g., the rabbit β -globin regulatory elements), constitutively active promoters (e.g., the β-actin promoter, etc.), signal specific promoters (e.g., inducible promoters such as a promoter responsive to RU486, etc.), and tissue-specific promoters (e.g., those active in epidermal tissue, dermal tissue, tissue of the digestive organs (e.g., cells of the esophagus, stomach, intestines, colon, etc., or their related glands), smooth muscles, such as vascular smooth muscles, cardiac muscles, skeletal muscles, lung tissue, hepatocytes, lymphocytes, endothelial cells, sclerocytes, kidney cells, glandular cells (e.g., those in the thymus, ovaries, testicles, pancreas, adrenals, pituitary, etc.). tumor cells, cells in connective tissue, cells in the central nervous system (e.g., neurons, neuralgia, etc.), cells in the peripheral nervous system, and other cells of interest).

The isolated or substantially purified nucleic acid of the present invention encodes all or part of a T-type calcium channel α subunit. As used herein, a "calcium channel" includes a protein structure for facilitating the flux of calcium ions across a biological membrane into which the calcium channel is inserted. As used herein, a "T-type channel" is a type of voltage-gated ion channel that facilitates the flux of ions

when the membrane potential of a biological membrane into which it is inserted experiences a slight depolarization. Thus, a T-type calcium channel can begin to gate from about -60 mV to about -30 mV (i.e., about -45 mV to about -35 mV) in about 10 mM Ba²⁻. Additionally, T-type channels of the present invention exhibit a slow deactivation (tail current) following depolarization. Thus, a T-type calcium channel can exhibit a tail current that decays exponentially with a tau value from about 1 ms to about 10 ms (e.g., from about 4 ms to about 7 ms, such as about 6 ms) following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a Ba²⁺ concentration of from about 10 mM to about 40 mM. Another defining characteristic of T-type calcium channels is that they exhibit small single channel conductance. Thus, for example, a T-type channel exhibits a single channel conductance of from about 4 pS to about 12 pS (e.g., from about 6 pS to about 10 pS), and typically from about 7 pS to about 9 pS in a solution with a Ba²⁺ concentration of about 0.1 M.

The isolated or substantially purified nucleic acid of the present invention encodes all or part of any T-type calcium channel having at least one of the aforementioned electrophysiological properties when properly assembled within a cellular membrane. The general structure of calcium channels is summarized above and is otherwise known in the art. Thus, for example, the nucleic acid can encode one of the four functional domains mentioned above. As used herein, a domain of a Ttype calcium channel is any protein structure able to associate with three other domains to form a tetrameric body functioning as a T-type calcium channel. While the native T-type calcium channel structure includes all four domains in a single polypeptide (indicated in Figures 1A-1E), a domain can exist as a polypeptide species separate from those containing the other domains. Such separate domains are able to associate within the plasma membrane to form a functional channel. Alternatively, where a plurality of domains are linked within a common polypeptide, the linkage can deviate substantially from the native linkage. Thus, for example, the domains can be linked by polypeptide sequences other than those sequences linking the domains in the native protein (e.g., non-native polyglutamate linkages). Indeed, the domains themselves can include non-native linkages between membrane-spanning elements within the domains. Aside from these modifications, the nucleic acid can encode a chimeric calcium channel domain (or an entire channel) comprising a portion of a Ttype calcium channel and a portion derived from another calcium channel (or other channel) protein. For example, the chimera can include portions of domains from Ttype channels responsible for low voltage gating and portions of domains from other calcium channels responsible for slow inactivation. Such a protein exhibiting T-type gating but longer inactivation kinetics would facilitate pharmacological research.

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As mentioned, nucleic acids of the present invention can encode an entire Ttype channel (i.e., a T-type channel protein comprising four functional domains). It has been discovered that at least three genes encoding T-type calcium channels exist in humans and rats (i.e., α 1G (or Ca,T.1), α 1H (or Ca,T.2), and α 1I (or Ca,T.3)), and alternate splicing of these isoforms exist. Examples of the amino acid sequences of full-length T-type channels, and the sequences of suitable coding nucleic acids are set forth at SEQ ID NOs:1-8 (a1G sequences). SEQ IS NOs:9-10 (a1H sequences), and SEQ ID NOs: 11-12 (α 11 sequences). However, the invention is not limited to these exemplary sequences. Indeed, as mentioned, an amino acid sequence of a T-type calcium channel can vary from those listed, and it is within the state of the art to change a nucleotide sequence encoding a T-type channel to introduce mutations into the protein. Indeed, for conducting electrophysiological assays, it may be desirable to introduce mutations into such a protein. For example, mutations comprising insertions or deletions can be introduced on either the amino- or carboxy-terminus of the protein, or such mutations can be intrasequence insertions or deletions. Where the electrophysiological properties of the calcium channel are to be conserved, such mutations preferably are in regions other than the membrane spanning domains. However, in some applications (e.g., to decrease inactivation kinetics), the changes can be within the membrane-spanning regions. Moreover, as mentioned above, the sequence can form a protein having only one functional domain of a T-type calcium channel. Additionally, the sequence can also form a chimeric protein or domain, such as those described above.

Aside from insertions and deletion mutations of native T-type calcium channel sequences, a T-type calcium channel can include substitutions of amino acid residues, e.g., for those indicated in SEQ ID NOs:1-12. Preferably, and especially where such a substitution is within a membrane spanning region, the substitution is conservative. Thus, within membrane spanning domains, positively-charged residues (H, K, and R) preferably are only substituted with positively-charged residues; negatively-charged residues (D and E) preferably are only substituted with negatively-charged residues; neutral polar residues (C, G, N, Q, S, T, and Y) preferably are only substituted with neutral polar residues; and neutral non-polar residues (A, F, I, L, M, P, V, and W) preferably are only substituted with neutral non-polar residues. Preferably, any amino-acid substitution within the membrane-spanning regions does not alter this conservation. Most preferably, any substitution, deletion, or insertion does not alter the IVS4 domain. In each of the exemplary T-type calcium channel α subunit sequences, the putative IVS4 region comprises SEQ ID NO:13. Given the strong sequence conservation among families of voltage-gated ion channels, it is likely that this sequence or a derivative sequence, will be present in T-type channels. Thus, the

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present invention provides any T-type calcium channel (or a nucleic acid encoding such a T-type calcium channel) comprising SEQ ID NO:13 or a sequence derived from SEQ ID NO:13 having conservative amino acid substitutions. as described above.

The nucleic acid of the present invention encoding all or a part of a T-type calcium channel can be isolated via any suitable method. For example, prior to the present invention, one of skill in the art could design a probe based on the sequence of known, non-T-type, calcium channels and use such probe to screen a genetic library. If such a screen were to identify a putative calcium channel, the researcher could then attempt to clone the entire nucleic acid to characterize it. Similarly, prior to the present invention, to isolate a nucleic acid encoding a T-type calcium channel, one of skill in the art could consult publicly available databases containing DNA sequences (e.g., Genbank) to locate nucleic or amino acid sequences representing a portion of a T-type calcium channel protein or nucleic acid. However, such databases contain no sequence for a full-length T-type calcium channel or identify any sequence as a T-type channel. Such methods assume that T-type calcium channels share sufficient sequence identity with known calcium channel nucleic acids to cross-hybridize, an assumption not supported by any published report. Moreover, prior to the present invention, no partial sequence in such databases was identified as corresponding to a T-type calcium channel. Thus, prior to the present invention, the presence of partial sequences in the public DNA databases could facilitate the isolation of T-type calcium channels only with the exercise of a considerable degree of speculation on the part of the researcher.

By providing several sequences pertaining to T-type calcium channels and a comparison presenting conserved regions and domains, the present invention greatly facilitates the isolation of other nucleic acids encoding T-type calcium channels (or derivatives thereof) with much less experimentation. Thus, while any of the methods discussed above can be employed to isolate other members of this genus, preferably, a nucleic acid encoding a T-type calcium channel is isolated by probing a genetic library using a probe that hybridizes to a DNA encoding a peptide sequence contained in (or similar to) a known T-type calcium channel (e.g., SEQ ID NOs:1-12). To facilitate the isolation of a T-type calcium channel, the present invention provides an isolated polynucleotide hybridizing to a portion of the nucleic acid of the present invention encoding a T-type calcium channel (or a portion thereof). Thus, for example, the present invention includes an isolated polynucleotide hybridizing to SEQ ID NO:1-12. The isolated polynucleotide can hybridize to all or any portion of the sequence encoding the T-type calcium channel.

To isolate such a polynucleotide, any portion of a sequence encoding a T-type calcium channel can be employed as a probe to screen a genetic library, and such screening can be accomplished by standard techniques known in the art. While the probe can hybridize to any portion of such a DNA, preferably the probe is designed to hybridize to a DNA encoding a polypeptide sequence that is highly conserved among T-type calcium channels but is less conserved between the genus of T-type calcium channels and other proteins. Such peptide sequences are readily apparent from the sequence comparison set forth in Figures 1A-1E. Generally, the specificity of hybridization in a genetic screen varies depending on the length of the probe and the stringency (e.g., temperature, salt and detergent concentration, etc.) of hybridization. Stringency of hybridization is broadly classified as "high," "moderate," or "low," and the parameters of these terms are well recognized in the art (see, e.g., Sambrook et al., "Molecular Cloning, a Laboratory Manual," Cold Spring Harbor Press, 1989). The isolated polynucleotide hybridizing to a portion of the nucleic acid encoding a T-type calcium channel can hybridize under any desired stringency conditions. However, for identifying other T-type channels, preferably, the hybridization occurs under moderate stringency, and most preferably under high stringency.

Of course, the isolated or substantially purified polynucleotide can itself be employed as a probe to screen a library as described to isolate a second nucleic acid. In such a screen, one of the polynucleotides will be complementary to a portion of the sequence encoding the T-type calcium channel, and the other isolated nucleic acid will be "sense." Preferably, one of the two isolated polynucleotides (the "sense" strand) itself encodes a T-type calcium channel, or at least one domain thereof. Such a sequence can be cloned to be operably linked to suitable regulatory elements, as described, to produce a T-type calcium channel. Thus, aside from using the nucleic acid of the present invention to produce a T-type calcium channel, the nucleic acids of the present invention are also useful for isolating other sequences encoding T-type calcium channels, or derivatives thereof.

However isolated, the isolated or substantially purified nucleic acid of the present invention is useful. in part, for producing all or a portion of a T-type calcium channel. Thus, the nucleic acid can be introduced into a suitable milieu for driving its expression. Because T-type channels are transmembrane proteins, preferably such a milieu is a living cell. However, it should be understood that the nucleic acid can also be expressed *in vitro* under conditions, such as those known in the art, suitable for *in vitro* transcription and translation. However produced, the present invention includes any protein, such as a recombinant protein or an isolated or substantially purified protein, including all or a portion of a T-type calcium channel or a protein derived from a T-type calcium channel.

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For expression in a living cell, the nucleic acid must be introduced into the cell. As nucleic acids are generally introduced into cells as part of genetic vectors, the present invention provides a vector having a T-type calcium channel nucleic acid of the type described above. Any type of vector suitable for introducing the nucleic acid into a host cell is within the context of the present invention. Examples of such vectors include naked DNA and RNA vectors (such as oligonucleotides, plasmids, capped cRNA, etc.), viral vectors such as adeno-associated viral vectors (Berns et al., *Annals of the New York Academy of Sciences*, 772, 95-104 (1995)), adenoviral vectors (Bain et al., *Gene Therapy*, 1, S68 (1994)), herpesvirus vectors (Fink et al., *Ann. Rev. Neurosci.*, 19, 265-87 (1996)), packaged amplicons (Federoff et al., *Proc. Nat. Acad. Sci. USA*, 89, 1636-40 (1992)), pappiloma virus vectors, picornavirus vectors, polyoma virus vectors, retroviral vectors, SV40 viral vectors, vaccinia virus vectors, and other vectors. Once a given type of vector is selected, its genome must be manipulated for use as a background vector, after which it must be engineered to incorporate exogenous polynucleotides. Such manipulations are known in the art.

The vectors of the present invention are useful for introducing a nucleic acid encoding all or a portion of a T-type calcium channel into a host cell. Thus, the present invention provides a cell into which the vector of the present invention has been introduced. The host cell can be any cell suitable for expressing the nucleic acid (e.g., bacteria, insect cells, mammalian cells, etc.). The host cell can thus be *in vitro* or *in vivo*. Preferably the cells do not exhibit native T-type calcium current. A preferred cell type is HEK-293 cells because they contain genetic elements that facilitate the expression of transgenes from a variety of expression vectors. For facilitating electrophysiological recordings, oocytes (e.g., *Xenopus* oocytes) are preferred, as they are large and readily handled.

The vector can be introduced into the cell in any manner suitable for the cell type and vector employed. In one embodiment, the vector can be used to prepare an RNA transcript *in vitro* (e.g., a capped cRNA) which is then introduced into the host cell by standard methods (such as injection). Such techniques are preferred when the host cells do not actively transcribe DNA (such as oocytes). In other embodiments, a DNA vector is introduced into the cell such that it is transcribed within the cell. For example, the vector can be introduced into the cell such that it forms an extrachromosomal segment of genetic material in the cell, as is the case with many types of viral vectors. Alternatively, the vector can introduce the nucleic acid into the chromosomal DNA of the host cell.

Preferably, a cell into which the nucleic acid is introduced is also able to express the nucleic acid to produce the α subunit protein. The expression of the nucleic acid can be detected by probing the cell for the presence of T-type calcium

channel mRNA, such as via Northern hybridization analysis, in situ hybridization, etc. More preferably, however, the cell is able to express the nucleic acid to produce the protein including all or a portion of a T-type calcium channel. In such cells, expression of the nucleic acid is confirmed by detecting the protein, for example, by probing cellular extracts with an antibody recognizing the protein (e.g., on a Western blot, etc.).

In the membrane of the cell producing the protein, the expressed protein contributes to the formation of a functional calcium channel. Where the protein encodes an entire α subunit, the full protein will possess some or all of the electrophysiological properties of T-type calcium channels described above. Where the protein encodes less than an entire channel α subunit (e.g., a domain), the protein will aggregate with other constituent domains in the membrane to form a functional channel. Thus, the presence of the protein can be detected by assaying the cell for T-type calcium channel activity. Indeed, assaying for channel activity serves to determine whether a nucleic acid encoding a putative calcium channel, in fact, encodes a species of T-type channel (as opposed to a member of another genus of calcium channels). For example, when large cells (e.g., oocytes) are used as the host cells, the electrophysiological properties of the channel can be investigated. Thus, the membrane activity of whole cells expressing the nucleic acid can be measured directly, such as via patch clamp techniques using a voltage clamp electrode and a current electrode (Bernal et al., J. Pharmacol. Exp. Ther., 282, 172-80 (1997)). Alternatively, the activity of single channels can be measured, such as with a standard depolarizing bath and pipette solutions (Lacerda et al., Biophys. J., 66, 183-43 (1994)). However measured, the properties of cells into which the putative nucleic acid is introduced are compared to the channel conductance, voltage dependency. activation kinetics, inactivation kinetics, or tail current known for T-type channels and discussed above. A measure of current density (e.g., pA/pF) can also be used to assess the level of gene expression in the cells, normalizing for cellular volume.

While, in accordance with the present invention, an isolated cell into which the T-type calcium channel nucleic acid has been introduced (and preferably stably expressing the nucleic acid to produce the protein) can be prepared, preferably, such transfection protocols result in a population consisting essentially of such transfected cells. For standardizing the results of many experiments, it is even more desirable to employ an established cell line consisting essentially of such cells. Preferably, for use in high throughput assays, cell lines stably expressing a T-type calcium channel exhibit a current density of at least about 40 pA/pF (e.g., at least about 45 pA/pF), such as about 50 pA/pF or even 55 pA/pF or higher. Preferably, a cell line in accordance with the present invention is able to propagate the nucleic acid through

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several passages (e.g., for at least 10 passages), and, preferably, the nucleic acid is stably integrated into the chromosomes of such cells. Thus, the cell line can propagate the nucleic acid for at least 20 passages, and more preferably significantly more than 20 passages (e.g., at least about 25 passages, or even more).

Regardless of the cell system, the ability to express a T-type calcium channel nucleic acid within host cells to produce an active channel permits the channel to be further studied. In this regard, the present invention provides a method of identifying a drug which affects T-type calcium channels. The method involves first expressing a T-type calcium channel in a cell to produce an active channel, as herein described. The cell expressing the channel is then exposed to a solution containing a putative drug for interfering with the channel. Thereafter, the presence or absence of calcium flux in response to a change in membrane potential is assayed. Any such assay can be employed within the context of the present invention, (e.g., using labile dyes, radioisotopes (e.g., ⁴⁵Ca), recording electrophysiological changes in the membrane, etc.). A quick method of assaying for calcium flux is first to introduce a calcium-sensitive labile dye into the cells. For example, the dye can be one such as those that fluoresce or change color in the presence of calcium, many of which are known to those of skill in the art (e.g., Indo-1). Thereafter, the cells are exposed to a depolarizing solution containing high (e.g., about 50 mM) potassium concentration and a drug, and the reaction of the labile dye is compared to control cells. Using a labile dye affords the ability to assay many putative drugs quickly in a high throughput assay for putative drugs affecting T-type channels. For example, the initial screening can be carried out in 96 well plates. Moreover, dose-response data can be readily generated by exposing the cells to several concentrations of the same putative drug.

Once a putative drug is detected, its effect on the electrophysiology of the cell (e.g., single channel conductance, voltage dependency, activation kinetics, inactivation kinetics, and tail current of the cells) can be investigated in detail. Generally, the effect of the putative drug on T-type calcium currents is assessed by measuring the various electrophysiological parameters in the presence of various concentrations of the drugs and comparing the data to untreated (or sham-treated) control cells. Cells preferably are maintained in a continuous perfusion chamber during such experiments to facilitate changing solutions. The inventive method of identifying a drug which affects T-type calcium channels can employ any nucleic acid encoding a T-type calcium channel (or derivative thereof), such as those nucleic acids described herein. In fact, as several isoforms of T-type channel exist, the assay method can be repeated using nucleic acids encoding different isoforms to identify

drugs that preferentially target a given isoform, or drugs which affect more than one isoform of T-type calcium channels.

Aside from affording an in vitro assay for detecting potential therapeutic or investigative drugs targeting T-type calcium channels, the method of expressing the T-type calcium channel nucleic acid can also be used in vivo. For example, as mentioned, several neurological and muscular diseases or disorders have implicated mutations affecting native nucleic acids encoding T-type calcium channels. The present invention, thus, provides a method of treating a disease or disorder associated with a deficiency in a native T-type calcium channel nucleic acid. The method involves introducing a vector having the T-type calcium channel nucleic acid into cells of a host in which native expression of the nucleic acid is deficient. Thus, for example, for treating cardiomyopathy associated with deficiencies in T-type calcium channels, the vector is introduced into myocardial cells. Similarly, for treating forms of epilepsy associated with deficiencies in T-type calcium channels, the vector is introduced into neurons (e.g., thalamic neurons). Within the target cells, the nucleic acid within the vector is expressed to produce active T-type calcium channel. By similar methods, an nucleic acid having a sequence antisense to a sequence encoding a T-type calcium channel (or a portion thereof) can be expressed within a cell. The presence of an antisense sequence can down-regulate the expression of native T-type calcium channel genes by hybridizing to T-type channel mRNA within the cell. Thus, the present invention is useful to treating disorders associated with over-expression of T-type calcium channels.

T-type channel proteins (such as whole T-type calcium channels, domains of such channels, chimeras including portions of T-type calcium channels, etc.) can be employed to generate antibodies (e.g., immunoglobulins) to T-type calcium channels. Thus, the present invention provides an isolated and substantially purified antibody molecule recognizing an epitope on a T-type calcium channel. Such antibodies can be monoclonal antibodies or polyclonal antisera. Antibodies recognizing T-type calcium channels can be used to purify the channels from cell extracts or other solutions by standard methodologies (e.g., immunoprecipitation). Moreover, depending on the location of the epitopes for the antibodies on the T-type calcium channel, the antibodies can be used to affect the channel proteins present on the surface of cells. Thus, antibodies directed to T-type calcium channels are potential reagents for studying the channels as well as for therapy.

Such antibodies can be produced by any suitable method, many of which are well known in the art. Thus, for example, the antibodies can comprise polyclonal antisera obtained from innoculated animals. Alternatively, the antibody molecules can be monoclonal antibodies obtained from a cell line (e.g., a hybridoma cell line). Thus,

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the present invention provides a cell which produces such antibodies. Such a cell can be *in vitro* or *in vivo*; however, where the cell is *in vitro*, preferably it is within an established cell line consisting essentially of such cells.

Several examples are presented below to illustrate the invention. Taken together, the examples demonstrate the cloning of twelve novel proteins and their characterization as T-type calcium channel α subunits. These examples are included here for purely illustrative purposes; as such, they are not to be construed so as to limit the scope of any aspect of the invention.

Many procedures employed in the following examples are techniques routinely performed by one of ordinary skill in the art (see generally Sambrook et al., *Molecular Cloning*. A Laboratory Manual, Cold Spring Harbor Laboratory. Cold Spring Harbor, NY (1989)) and are not discussed in detail. However, some reagents and methods deserve specific description. Thus, for example, in vitro translation and expression were conducted as described previously (Schneider et al., Receptors and Channels, 2, 255-70 (1995)). Xenopus laevis oocytes were prepared as described previously (Bernal et al., J. Pharmacol. Exp. Ther., 282, 172-80 (1997)). To express proteins, 10 or 30 ng of capped cRNA was injected into the oocytes in a volume of 50 nl. For single channel recording, oocytes were injected with 100 ng capped cRNA and incubated for one week prior to assay.

Cells were voltage clamped using a two-microelectrode voltage clamp amplifier as described (Bernal et al., *J. Pharmacol. Exp. Ther., 282*, 172-80 (1997)). The standard bath solution contained the following: 40 mM Ba(OH)₂, 50 mM NaOH, 1 mM KOH, 0.1 mM EDTA, and 5 mM HEPES, adjusted to pH 7.4 with methanesulfonate. The osmolality of the 2 mM Ba²⁺ and 10 mM Ba²⁺ solutions was balanced by increasing the NaOH concentration as described (Lory et al., *J. Physiol., (London), 429*, 95-112 (1990)). Voltage and current electrodes (1.5-1.8 M tip resistance) were filled with 3 M KCl. Except as noted, data were acquired at 4 kHz using the pCLAMP system, and filtered at 1 kHz. Data were analyzed using pCLAMP software. Boltzman fits and linear regression were calculated using Prism.

EXAMPLE 1

This example demonstrates the cloning and characterization of putative T-type calcium channels.

A search of the Genbank library was conducted to identify clones identified as having some degree of homology to known calcium channel sequences. The search identified an expressed sequence tagged (EST) partial sequence in a human brain clone (H06096), which was used as a probe to screen a \(\lambda\)gt10 cDNA library prepared

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from rat brain. Successive screening of the cDNA library identified five overlapping clones which were aligned to construct an entire cDNA sequence, termed $\alpha 1G$.

The $\alpha 1G$ cDNA was cloned into the pSP72TM vector and sequenced by standard computer-assisted sequencing. Using the $\alpha 1G$ cDNA, the amino acid sequence of the $\alpha 1G$ protein was deduced and compared to the sequences of other known calcium channel α subunits. By similar methods, homologous human (H19230 and R19524) and mouse (AA286626) EST clones were also identified and partially sequenced, and alternately spliced variants were identified. The deduced cDNA and amino acid sequences for eight full-length $\alpha 1G$ T-type channels are set forth, respectively, as SEQ ID NOs:1-8.

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A second T-type calcium channel, termed $\alpha 1H$, was isolated by screening a human heart cDNA library with a fragment of the $\alpha 1G$ sequence. An alternately spliced isoform was also identified. The full-length cDNA and amino acid sequences for these $\alpha 1H$ T-type channels are set forth, respectively, as SEQ ID NOs:9 and 10.

A third T-type calcium channel, termed $\alpha 1I$, was isolated by screening a rat brain cDNA library at low stringency using a fragment of the rat $\alpha 1G$ gene. Fifty plaques were identified, many of which were not detected in a second screening. A third screening with a fragment from $\alpha 1H$ identified two clones. Subsequent screening, and the use of the GenBank database, led to the identification of the full length rat and human cDNA and amino acid sequences, set forth at SEQ ID NOs: 11 and 12, respectively.

The α 1G, α 1H, and α 1I amino acid sequences were compared to each other and a known calcium channel (α 1E) to investigate the conservation of protein structure and function. The comparison indicates that the α 1G, α 1H, and α 1I amino acid sequences within the putative membrane-spanning domains are about 90 % identical to each other, while the α 1G, α 1H, and α 1I sequences are only roughly 40 % identical to the α 1E clone.

Figures 1A-1E indicate this conservation between the proteins. The conservation of charged residues, particularly in the S4 domains, is consistent with the role of the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins as ion channels. However, two of the glutamates associated with ion specificity in other calcium channels have been replaced with aspartate, suggesting altered ion selectivity. Strikingly, $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ display only low homology to sequences linking the membrane-spanning regions within each domain, and even less homology between the intracellular loops linking domains. Notably, neither $\alpha 1G$, $\alpha 1H$, nor $\alpha 1I$ possesses sequences known to bind β subunits or Ca^{2+} ions.

EXAMPLE 2

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This example demonstrates the production of cell lines stably expressing the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins.

HEK-293 cells were transfected with either the rat α1G cDNA (SEQ ID NO:1). the human α1H cDNA (SEQ ID NO:9), or the rat α1I cDNA (SEQ ID NO:11). As a control, cells were also transfected with human α1E plus human β3 (Schneider et al., *Receptors Channels*, 2, 255-70 (1994); Murakami et al., *Eur. J. Biochem.*, 236, 138-43 (1996)). The DNA constructs included a neomycin resistance gene conferring resistance to G418. The cells were cultured under standard conditions using medium containing G418 to select for stable transformants.

Surviving clones were expanded and assayed for electrophysiological activity to determine the presence of channels within the membrane. Whole-cell currents were recorded from ruptured patches using an Axopatch 200A amplifier. Digidata 1200 A/D converter, and pCLAMP 6.0 software. Data were digitized at 2 kHz and filtered at 1 kHz or off-line. All experiments were performed at room temperature. Pipettes were made out of TW-150-6 capillary tubing (World Precision Instruments, Inc., Sarasota, FL), using a Model P-97 Flaming-Brown pipette puller (Sutter Instrument Co., Novato, CA). The internal pipette solution contained the following: 55 mM CsCl, 75 mM CsSO₄, 10 mM MgCl₂, 0.1 mM EGTA, 10 mM HEPES, pH adjusted to 7.2 with CsOH. The external Tyrodes solution was the following: 140 mM NaCl, 6 mM KCl, 2 mM CaCl₂, 10 mM glucose, 5 mM HEPES, pH 7.4. The recording solution contained the following: 10 mM BaCl₂ solution (or 2 mM CaCl₂), 140 mM tetraethylammonium (TEA) chloride, 5 mM CsCl, 1 mM MgCl₂, 5 mM glucose, and 10 mM HEPES, pH adjusted to 7.4 with TEA-OH. Under these solution conditions the pipette resistance was typically 1.5-2.5 M Ω . Cell capacitance was measured by integrating the charging current during a 10 mV hyperpolarizing pulse (holding potential -80 mV).

Using these recording techniques, values for pA/pF were obtained for each cell line, which is a measure of current density normalizing for cell size. One clone (#N2) expressed the rat α 1G protein and has a current density of 42 pA/pF. Another clone (#13), expressed the human α 1H protein and exhibited a current density of 53 pA/pF. Three clones (#11, #19, and #25) expressed the rat α 1I protein and exhibited current densities of 40 pA/pF, 45 pA/pF, and 55 pA/pF, respectively

35 EXAMPLE 3

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type current-voltage relationships.

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Current traces were elicited by depolarizing voltage clamp pulses of the membranes of cells. The α 1G, α 1H, and α 1I proteins were produced in *Xenopus laevis* oocytes by linearizing the DNA vectors containing the coding sequences, and transcribing the coding sequences *in vitro* by standard methods. Oocytes were then injected with the capped RNA.

Figures 2A-2E depict data obtained from these experiments using cells injected with $\alpha 1G$ (Figure 2A), $\alpha 1H$ (Figure 2B), and $\alpha 1I$ (Figure 2C) and $\alpha 1E$ (Figure 2D). These data indicate that cells expressing $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ exhibit T-type calcium current, while oocytes expressing $\alpha 1E$ as well as uninjected oocytes (Figure 6A) do not.

Current voltage curves were developed using cells injected with $\alpha 1G$, $\alpha 1H$, $\alpha 1I$, and $\alpha 1E$. Figures 3A depicts such data generated in a 10 mM Ba²⁺ test solution. These data were transformed into conductance and fit with a Boltzman equation to determine the midpoint of activation (V_{0.5}). Gating potentials for $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ (-38 ± 1 mV n=8, -44 mV ± 1 mV, n=10, and -31 mV ± 1 mV, n=6, respectively) were in accordance with the gating potential measured for the HEK-293 cells (-41 ± 1 mV, n=10), while $\alpha 1E$ required significantly more positive potentials to open (-2.6 mV ± .4 mV, n=3).

To compare the characteristics with published values (Huguenard, Ann. Rev. Physiol., 58, 329-48 (1996)), the α1G current was recorded at varying concentrations of Ba²⁺. As indicated in Figure 3B, in solutions containing 2 mM Ba²⁺, V_{0.5} was -46.5 mV, and the slope factor (k) was 6.6 (n=7). However, when the Ba²⁺ concentration was 40 mM, V_{0.5} was recorded at -21 mV, presumably due to the results of barium on surface charge screening (see, e.g., Wilson et al., J. Membrane Biol., 72, 117-30 (1983)). Similar values were recorded for α1H and α1I.

These results indicate that $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ are low-voltage activated calcium channels (i.e., from about -60 mV to about -30 mV in 10 mM Ba²⁺).

EXAMPLE 4

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This example demonstrates that the cloned putative T-type calcium channels exhibit T-type tail current.

Tail current was measured at -90 mV after first opening the channels with a voltage step to -10 mV. The voltage-dependence of tail current in cells expressing $\alpha 1G$ (oocytes) $\alpha 1H$ (HEK 293 cells), and $\alpha 1I$ (HEK 293 cells) was measured at varying test potentials. As a control, tail current was also measured from a high voltage activated channel $\alpha 1E$, which Raw data from recordings data were fit with a single exponential and plotted as a function of depolarization potential (Figure 4).

These results demonstrate that the tail currents for the cloned $\alpha 1G$. $\alpha 1H$. and $\alpha 1I$ calcium channels are voltage-dependent, consistent with known T-type calcium tail currents. Additionally, these data demonstrate that the tail current for each of the cloned channels is between about 1 ms and about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.

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EXAMPLE 5

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This example demonstrates that the cloned putative T-type calcium channels exhibit T-type single channel conductance.

Measurement of single channel conductance is complicated by the low probability of channel opening at negative potentials when the driving force is large. Thus, single channel conductance was measured similarly for measurements of tail currents to enhance channel opening at negative potentials. Single channels were measured with standard depolarizing bath and pipette (115 mM BaCl₂, 1 mM EGTA, and 10 mM HEPES, pH 7.4) solutions (Lacerda et al., *Biophys. J.*, 66, 1833-43 (1994)). Data were analyzed with TRANSIT (VanDongan, *Biophys J.*, 70, 1303-15 (1996)). Single channel amplitudes were measured by averaging the values obtained from Gaussian fits to all-points histograms of traces with openings, selected openings, or amplitude histograms of idealized openings. It has been reported that some oocytes contain a native 9 pS channel. These endogenous channels can be distinguished by their 2-fold larger current amplitudes at the potentials tested (e.g., -20 mV, i = 0.8 for endogenous channels as opposed to 0.4 pA for α 1G). However, such endogenous channels were not detected either at the whole cell or single channel level in the oocytes tested.

Current through the main open state of each open channel was measured at each potential and plotted against each test potential. Single channel currents for several patches were then averaged and plotted as a function of test potential, wherein the slope of the plot indicated the single channel conductance. The average slope conductance of the $\alpha 1G$ channel was measured at 7.5 ± 1.5 pS, which corresponds with the reported values for T-type calcium channels (Hugenard, *Ann. Rev. Phsysiol.*, 58, 329-48 (1996)). Similar results were also obtained with both $\alpha 1H$ (10.8 ± 1.4 pS). Data collected from recordings of the $\alpha 11$ channels indicate that they open to two distinct amplitudes. The conductance for the small amplitude $\alpha 11$ openings was measured at 3.9 ± 0.5 pS, while that for the large $\alpha 11$ openings was measured at 11.4 ± 0.5 pS).

These results indicate that the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins exhibit T-type single-channel conductance (e.g., from about 4 to about 12 pS).

EXAMPLE 6

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This example demonstrates that a cloned T-type calcium channel can be used for identifying a drug which affects T-type calcium channels.

HEK-293 cells were subjected to treatment as indicated above in Example 3, except that an experimental group of cells were exposed to a solution containing 1 μ M mibefradil, a known inhibitor of T-type calcium current. As depicted in Figure 5A, the presence of mibefradil almost completely abolished T-type current in cells expressing α 1G. Cells expressing either α 1G or α 1H were similarly treated using various concentrations of mibefradil to determine a dose-response relationship. These results, depicted in Figure 5B, demonstrate that about 50% inhibition was achieved at a mibefradil concentration of 1 μ M.

All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred embodiments may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

What is claimed is:

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- 1. A isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel α subunit.
- 2. The nucleic acid of claim 1, wherein said protein comprises an entire T-type calcium channel α subunit.
- 3. The nucleic acid of claim 2, wherein said protein comprises SEQ ID NO:13.
- 4. The nucleic acid of any of claims 1-3, wherein said calcium channel begins to gate from about -60 mV to about -30 mV in 2 mM Ba²⁺.
- 5. The nucleic acid of any of claims 1-4, wherein said calcium channel exhibits a tail current of from about 1 ms to about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.
- 6. The nucleic acid of any of claims 1-5, wherein said calcium channel exhibits a single channel conductance of from about 4 pS to about 11 pS in a solution with a barium ion concentration of about 100 mM.
 - 7. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of any of claims 1-6.
 - 8. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of claim 7.
 - 9. The nucleic acid of claim 8 comprising a sequence encoding at least one domain of a T-type calcium channel α subunit.
 - 10. A vector comprising the nucleic acid of any of claims 1-9.
 - 11. A cell into which the vector of claim 10 has been introduced.
 - 12. The cell of claim 11, which expresses said nucleic acid to produce said protein.
 - 13. The cell of claim 11 or 12, which stably expresses said nucleic acid to produce said protein.
 - 14. A population of cells consisting essentially of cells according to any of claims 11-13.
 - 15. An established cell line consisting essentially of cells according to any of claims 11-13.
- 16. A method of identifying a drug which affects T-type calcium channels, said method comprising expressing a T-type calcium channel in a cell, exposing said cell to a putative drug, and measuring the calcium flux through the membrane of said cell in response to a change in membrane potential.

- 17. The method of claim 16, wherein said calcium flux is assayed by using a calcium-sensitive labile dye within said cell.
- 18. The method of claim 16, wherein said calcium flux is assayed by measuring the electrophysiological properties of said cell.
- 19. The method of claim 16. wherein said calcium channel comprises SEQ ID NO:13.
- 20. An isolated or substantially purified immunoglobulin recognizing an epitope on a T-type calcium channel protein.
 - 21. A cell in vitro which produces the immunoglobulin of claim 20.
- 22. An established cell line consisting essentially of cells according to claim 21.

hcavt2a mtegaraadevrvplgrrpwpcgvgggvpge prgagtrggggfelgvspsespaaercaelgadeeqrvpypalaatvffclgqttrprswclrlvcnpw -----paaepgviteqpgrsppssppgleepldgadphvphpdlapiaffclrqitsprnwcikmvcnpw -----APEPG--ITEQPGPRSPPPSPPGLEEPLEGTNPDVPHPDLAPVAFFCLRQTTSPRNWCIKMVCNPW ---SFMRINDLSGAGGRPGPGSAEKDPGSADSEAEGLPYPALAPVVFFYLSQDSRPRSWCLRTVCNPW MADSNLPPSSAAAP----hCavIla MDEEEDGAGAEESGQPR---MAESASPPSSSAAA-hCavT3 rCavI3

FECVSMLVILLNCVTLGMYQPCDDMECLSDRCKILQVFDDFIFIFFAMEMVLKMVALGIFGKKCYLGDTWNRLDFFIVMAGMVEYSLDLQNINLSAIRTV FERISMLVILLNCVTLGMFRPCEDIACDSQRCRILQAFDDFIFAFFAVEMVVMVALGIFGKKCYLGDTWNRLDFFIVIAGMLEYSLDLQNVSFSAVRTV FERVSMLVILLNCVTLGMFRPCEDIACDSQRCRILQAFDDFIFAFFAVEMVVMVALGIFGKKCYLGDTWNRLDFFIVIAGMLEYSLDLQNVSFSAVRTV FEHVSMLVIMLNCVTLOMFRPCEDVECGSERCNILEAFDAFIFAVEMVIKMVALGLFGQKCYLGDTWNRLDFFIVVAGMÆYSLDGHNVSLSAIRTV FECVSMLVILLNCVTLGMYQPCDDMDCLSDRCKIMQVFDDFIFIFFAMEMVLKMVALGIFGKKCYLGDTWNRLDFFIVMAGMVEYSLDLQNINLSAIRTV hCavIla hCavT2a hCavT3 rCavT3

rvlrplkainrvpsmrilvnilldtippiepmignvlilcffvffifgiigvolwaglirnrcfleenftiogdva-lppyyopeeddempficslsgdngimg hCavTla RVLRPLRAINRVPSMRILVTLLLDTLPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLPENFSLPLSVD-LERYYQTENEDESPFICSQPRENGMRS RVLRPLRAINRVPSMRILVTLLLDTLPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLPENFSLPLSVD-LEPYYQTENEDESPFICSQPRENGMRS hcavt2a RVLRPLRAINRVPSMRILVTLLLDTLPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLDSAFVRNNNLTFLRPYYQTEEGEENPFICSSRRDNGMQK RVIRPLKAINRVPSMRILVNLLLDTLPMLGNVLLLCFFVFFIFGIIGVQLWAGLLRNRCFLEENFTIQGDVA-LPPYYQPEEDDEMPFICSLTGDNGIMG hCavT3 rCavT3

rcavīla crsvptirgeg-----gggppcsidyetynsssnītcvnwnqyyīncsagehnpfkgainfdnīgyawīaīfqvīīlegwdīmyfvmdahsfynfiyfī hcavt2a cshipgrrdvrmpctlgwea-ytqpqaegvgaarnacinwnqyynvcrsgdsnphngainfdntcyawiaifqvitlegwydimyyvwdahsfynfiyfi CHEIPPLKEQGRECCLSKDDVYDFGAGRQDLNASGLCVNWNRYYNVCRTGSANPHKGAINFDNIGYAWIVIFQVITLEGWVEIMYYVMDAHSFYNFIYFI CHE I P PLKE QGRECCL SKODVYD FGAGR QD LNA SGLCVNWNR Y YNVCR T GNAN PHKGA IN FDN I GYAG I VI F GVI TLEGWVE IMYYVMDAHS FYN FIYFI hcavila crsvpilrgdg-----gggppcgldyeaynsssnitcvnwnoyyincsagehnpfkgainfdnigyawiaifgvitlegwydimyfvmdahsfynfiyfi IP LOOP hCavT3 rCavT3

hcavīza lliivgsffminiclvviatofsetkoresolmreorarhisndstlasfsepgscyeelikyvghifrkvkrrslrlyarwosrwrkkvdpsavoggofp lcavīla iliivgsffminicivviatoffsetkoresolmreorvrflsnastlasfsepgscyeelikylivyiirkaarrlaqvsraigvraglisspvarsgoep ncavtla iliivgsfeminicivviatofsetkoresoimreorvrfisnastlasfsepgscyeelikylvyiirkaarrlaqvsraagvrvgilsspapiggoet LLIIVGSFFMINLCLVVIATQFSETKQREHRLMLEQRQRYLSS-STVASYAEPGDCYEEIFQYVCHILRKAKRRALGLYQALQSRRQ-------llingsffminlclvviatofsetkorehrimleororylss-stvasyaepgdcyeeifoyvchiirkakrralglyqalonrro-hCav_{T3} rCavT3

Fig. 1A

hCavT2a GHRQRRAGRHTASVHHLVYHHHHHHHHHHYHFSHGSPRRPGPEPGACDTRLVRAGAPPSPPSPGRGPPDAESVHSIYHADCHIEGPQERARVGTCRSHCRC rcavtla QPSGSCTRSHRRLSVHHLVHHHHHHHHHHYHLGNGTLRVPRASPEIQDRDANGSRRLMLPPPSTPTPSGGPPRGA------ESVHSFYHADCHLEPVRC hCavTla QAPPPRSPSEASGRTVGSGKVYPTVHTSPPPETLKEKALVEVAASSGPPTLTSLN-IPPGPYSSMHKLLETQSTGACQSSCKISSPCLKADSGACGPDSC rCavTla QAPPPRCPSEASGRTVGSGKVYPTVHTSPPPEILKOKALVEVAPSPGPPTLTSFN-IPPGPFSSMHKLLETQSTGACHSSCKISSPCSKADSGACGPDSC hCavT2a QPQAGHRAGHHELPHDPALRGGQRQRQRQPRTQGEVGRWTARHRGHGPLSLNSPDPYEKIPHVAGEHGLGQAPGHLSGLSVPCPLPSPPAGTLTCELKSC ------ALGPEAPARAFGPHAKEPRHYQLCPQHSPLDATPHTLVQPIPATLASDPASC ----AMGPGTPAPAKPGPHAKEPSHCKLCPRHSPLDPTPHTLVQPISAILASDPSSC hcaviia pycara-gageveladrempdsdseavyeftodaqhsdlrdphs-------rr-orr-orslgpdaepssvlafwrlicdterkivdskyfgrgim rcavtla pycart-gagepesadhvmpdsdseavyeftqdaqhsdlrdphs-------rrrqrslgpdaepssvlafwrlicdtfrkivdskyfgrgim PYCTRALEDPEGELSGSESGDSDGRGVYEFTQDVRHGDRWDPTRPPRATDTPGPGSPQRRAQQRAAPGEPGWMGRLWVTFSGKLRRIVDSKYFSRGIM PCCQHEDGRRPSGLGSTDSGQEGS-----GSGSSAGGEDEADGDGARSSEDGASSELGKEEEEEEQADGAVWLCGDVWRETRAKLRGIVDSKYFNRGIM PHCQHEAGRRPSGLGSTDSGQEGS-----GSGGSA--EAEANGDGLQSSEDGVSSDLGKEEEQE---DGAARLCGDVWRETRKKLRGIVDSKYFNRGIM hcavīla IAILVNTLSMGIEYHEQPEELTNALEISNIVFTSLFALEMLLKLLVYGPFGYIKNPYNIFDGVIVVISVWEIVGQQGGGLSVLRTFRLMRVLKLVRFLPA rcavtla lailvntlsmgieyheqpeeltnaleisnivftslfalemllkllvygpfgyiknpynifdgvivvisvweivgqqggglsvlrtfrlmRvlklvrfipa hCavT2a MAILVNTLSMGVEYHEQPEELTNALEISNIVFTSMFALEMLLKLLACGPLGYIRNPYNIFDGIIVVISVWEIVGQADGGLSVLRTFRLLRVLKLVRFLPA mailvntvsmgiehheqpeeltnileicnvvftsmfalemilklaafglfdylrnpynifdsiiviisiweivgqadgglsvlrtfrllrvlklvrfmpa mailvntvsmgiehheqpeeltnileicnvvftsmfalemilklaafglfdylrnpynifdsiiviisiweivgqadgglsvlrtfrllrvlklvrfmpa hCavtla QPSSSCSRSHRRLSVHHLVHHHHHHHHHHHHGNGTLRAPRASPEIQDRDANGSRRLMLPPPSTPALSGAPPGGA---rCavT3 hCavT3 rCavT3 hCavT3 rCavT3 rCavI3

rCavT1a LQRQLVVLMKTMDNVATFCMLLMLFIFIFSILGMHLFGCKFASERD-GDTLPDRKNFDSLLWAIVTVFQILTQEDWNKVLYNGMASTSSWAALYFIALMT hCavT2a LRRQLVVLVKTMDNVATFCTLLMLEIFIFSILGMHLFGCKFSLKTDTGDTVPDRKNFDSLLMAIVTVFQILTQEDWNVVLYNGMASTSSWAALXFVALMT

hCavīla LQRQLVVIMKTMDNVATFCMLIMLFIFIFSILGMHLFGCKFASERD-GDŢLPDRKNFDSLLWAIVTVFQILTQEDWNKVLYNGMASTSSWAALIYFIALMT

LRRQLVVIMKTMDNVATFCMLIMLEIFIFSILGMHIFGCKFSLRTDTGDTVPDRKNFDSLLMAIVTVFQILTQEDWNVVLYNGMASTSPWASLYFVALMT

rCavT3

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rCav'ila lfgDlecdethPceglgrhatfrnfgmafltlfrvstgdnwngimkDtlrdcDqest----cyntvispiyfvsfvltaqffvlvnvviavlmkhleesnke hCavI2a LFGRLECSEDNPCEGLSRHATFSNFGMAFLTLFRVSTGDNWNGIMKDTLRECSREDKHCLSYLPAPSPVYFVTFVLVPQFVLVNVVVAVIMKHLEESNKE LFGKLVCNDENPCEGMSRHATFENFGMAFLTLFQVSTGDNWNGIMKDTLRDCTHDERSCLSSLQFVSPLYFVSFVLTAQFVLINVVVAVIMKHLDDSNKE hCavTla LFGDLECDETHPCEGLGRHATFRNFGMAFLTLFRVSTGDNWNGIMKDTLRDCDQEST---CYNTVISPIYFVSFVLTAQFVLVNVVIAVLMKHLEESNKE LFGKLVCNDENPCEGMSRHATFENFGMAFLTLFQVSTGDNWNGIMKDTLRDCTHDERTCLSSLQFVSPLYFVSFVLTAQFVLINVVVAVIMKHLDDSNKE IVP LOOP hCavT3 rCavT3

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Fig. 1D

Fig. 1E

hca,tla dllaevsgpspplaraysfwgqsstqaqqhsrshskiskhmtppapcpgpepnwgkgppetrssleldtelswisgdllppggqeeppsprdlkkcysve hca,tla symcrhgstaegplghrgwglpkaqsgsvlsvhsqpadtsyilqlpkdaphllqphsaptwgtipklpppgrsplaqrplrrqaairtdsldvqglgsre SYMCRNGSTAERSLGHRGWGLPKAQSGSILSVHSQPADTSCILQLPKDVHYLLQPHGAPTWGAIPKLPPPGRSPLAQRPLRRQAAIRTDSLDVQGLGSRE rca,tia dilsevsgpscpltrsssfwggssiqvqqrsgiqskvskhirlpapcpglepswakdppetrssleidtelswisgdilpss-qeeplfprdikkcysve hca,tla AQSCQRRPTSWLDEQRRHSIAVSCLDSGSQPHLGTDPSNLGGQPLGGPGSRPKKKLSPPSITIDPPESQGPRTPPSPGICLRRRAPSSDSKDPLASGPPD rca,tla toscrrrpgfwideorrhsiavscidsgsopricpspssiggopiggpgsrpkkkisppsisidppesogsrppcspgvcirrrapasdskopsvsspld -----GPRLPTGSPGAPGRGPGGAGGGGDTDGGLCRRCYSPAQENLWLDSVSLIIKDS----------PLHALSPRGTARSPSLSRLLCRQEAVHTDSLKGRLTALGTPWILQSLVRKPR (SEQ ID NO:9) -----LEGELTIIDNLSGSIFHHYSSPAGCKKCHHDKQETGPRPSCWVTT (SEQ ID NO:11) ----LEGELTIIDNLSGSVFHHYASPDGCGKCHHDKQETGLHPSCWGMT (SEQ ID NO:12) SYMERPVVPASAPHPRPLQEVEMETYGAGTPLGSVASVHSPPAESCASLQIPLAVSSPARSGE---------GPRLPTSSPGAPGRGSGGAGAGGDTESHLCRHCYSPAQETLWLDSVSLIIKDS-rCa,Tla hCa,T2a hCa_vT2a rCa_vT3 hCa,T3 hCa,T3 rCa,T3

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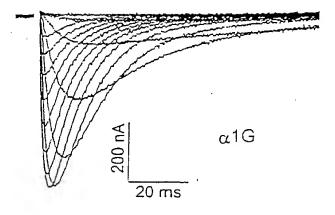


Figure 2A

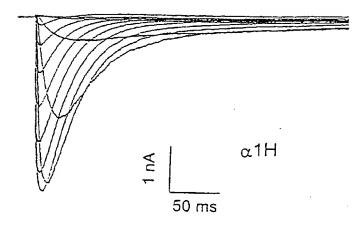


Figure 2B

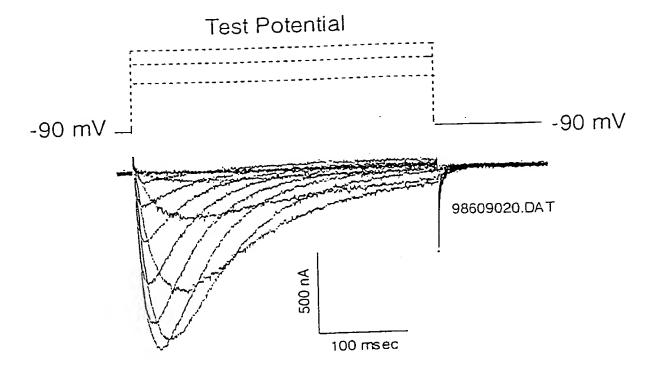


Figure 2C

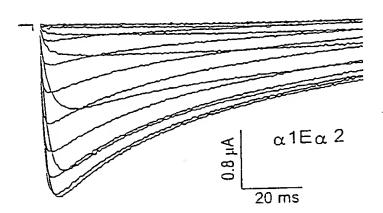


Figure 2D

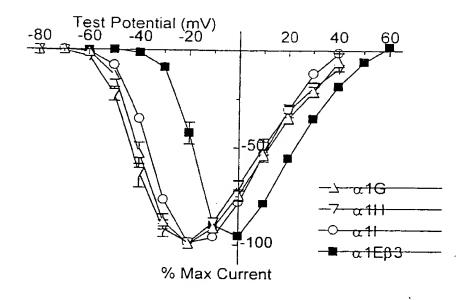


Figure 3A

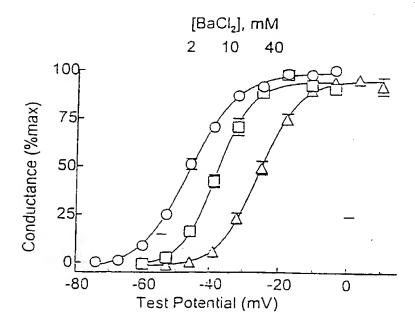


Figure 3B

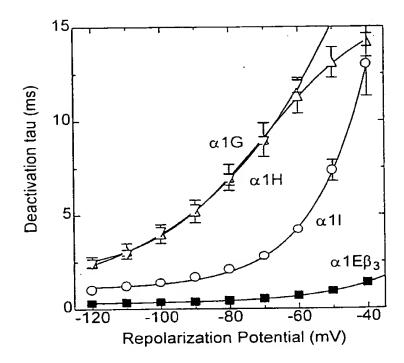


Figure 4

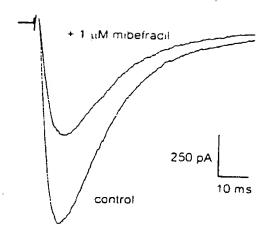


Figure 5A

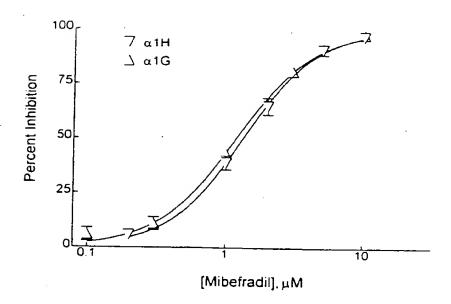


Figure 5B

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	acc c Thr L																336
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	Ala	Val 130	l Glu	ı Met	. Va.	l Val	L Lys 135	s Met	: Val	L Ala	: Let	Gl د 140	y Ile	∍ Phe	e Gly	/ Lys	
5	aaq Lys 145	, суз	tac Tyl	c cto	g gga u Gly	a gad / Asp 150	Thr	tg <u>c</u> Trp	j aac Asr	c ogç	g ctt Lei 155	ı Asp	tt! > Phe	tto Phe	ato e Ile	gtc Val 160	480
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20					gat Asp												2976
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50	Ser				gca Ala	Pro					Arg						3312
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15	gcc ga Ala As	1		1205	ASI.	ьес	. Sel	. Буз	1210) \ (1)	ı Arç	g Val	. Arq	2 Ala 121	a Trp	3648	
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15	ctg gat Leu Asp					Asp					Met					4464	
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35	cta cga Leu Arg	Arg					Arg					Lys				4656	
33	gaa gcc Glu Ala					Tyr					Ser					4704	
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	ttc cgt Phe Arg					Asp					Leu					4944	
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	gcc tcg	ctg	ccc	atc	aac	ccc	acc	atc	atc	cgc	atc	atg	agg	gtg	ctg	50.40	

	Ala Ser Le 1665	u Pro Ile	e Asn Pro 1670	o Thr Ile	e Ile Arq 1675	g lie Met	: Arg Va	l Leu 1680	
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10	gcg ctg ct Ala Leu Le	g gac aco u Asp Thr 1700	gtg ato Val Met	g cag gcd : Gln Ala 1705	a Leu Pro	cag gtg Gln Val	ggg aa Gly As 1710	c ctg n Leu	5136
15	gga ctt ct Gly Leu Le 171	a rne met	ttg ttg Leu Leu	ttt tto Phe Phe 1720	atc ttt Ile Phe	gca gct Ala Ala 1725	Leu Gl	c gtg y Val	5184
	gag ctc tt Glu Leu Pho 1730	t gga gac e Gly Asp	ctg gag Leu Glu 1735	Cys Asp	gag aca Glu Thr	cac ccc His Pro 1740	tgt ga Cys Gl	g ggc u Gly	5232
20	ctg ggc cg Leu Gly Arc 1745	a ura wra	acc ttt Thr Phe 1750	cgg aac Arg Asn	ttt ggc Phe Gly 1755	Met Ala	ttc ct Phe Le	a acc u Thr 1760	5280
25	ctc ttc cg: Leu Phe Arc	a gtc tcc g Val Ser 1765	Inr Gly	gac aat Asp Asn	tgg aat Trp Asn 1770	ggc att Gly Ile	atg aa Met Ly 177	s Asp	5328
30	acc ctc cgc Thr Leu Arc	g gac tgt g Asp Cys 1780	gac cag Asp Gln	gag tcc Glu Ser 1785	Thr Cys	Tyr Asn	acg gt Thr Va. 1790	c atc l Ile	5376
35	tcg cct ato Ser Pro Ile 1795	- rar tue	var Ser	ttc gtg Phe Val 1800	ctg acg Leu Thr	gcc cag Ala Gln 1805	ttc gto Phe Val	g cta l Leu	5424
	gtc aac gtc Val Asn Val 1810	g gtg atc Val Ile	gcc gtg Ala Val 1815	ctg atg Leu Met	Lys His	ctg gag Leu Glu 1820	gag ago Glu Sei	c aac c Asn	5472
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50	ctc tgg cct Leu Trp Pro	ggg gtc Gly Val 1860	gag ggc Glu Gly	ccc gac Pro Asp 1865	agc ccc Ser Pro	Asp Ser	ccc aag Pro Lys 1870	g cct Pro	5616
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	Pro Ash As	sp Ser Tyr Me 1925	et Cys Arg	His Gly Se 1930	er Thr Ala Glu	Gly Pro 1935
5			p Gly Leu		ct cag tca ggc la Gln Ser Gly 1950	
10		al His Ser Gl			gc tac atc ctg er Tyr Ile Leu 1965	
15					ac ago goo coa is Ser Ala Pro 1980	
15			eu Pro Pro		ge tee eet ttg cg Ser Pro Leu 95	
20					et gac toc ttg nr Asp Ser Leu	
25			g Glu Asp		ca gag gtg agt la Glu Val Ser 2030	
30		ro Leu Ala Ai		Ser Phe Tr	gg ggc cag tca rp Gly Gln Ser 2045	
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	aaa aaa ci	tc agc ccg c	ct agt ato	acc ata g	ac ccc ccc gag	agc caa 6576

	Lys Ly	s ĭe	u Se 218	r Pr O	o Pro	o Se	r Il	e Th: 218:	r Ile 5	e As	p Pr	o Pr	o Gl 219	u Se O	r Gln	
5	ggt co Gly Pr	t cg o Ar 219	9 111.	c cc r Pr	g ccc o Pro	age Se:	2 00: 2 Pro 2200	O (1)	t ato y Ile	e Cy	c ct s Le	c cge u Are 220!	g Ar	g ag g Ar	g get g Ala	6624
10	ccg tc Pro Se 221		c gad r Ası	c tco Se:	c aaq r Lys	g ga: 8 Ass 2215) PEC	c tro	g gcd 1 Ala	tc Se	t gg r Gl 222	y Pro	c cci	t ga. o As	c agc c Ser	6672
15	atg gc Met Al 2225	t gce a Ala	c too a Ser	g cco	tcc Ser 2230	PIC	a aaq D Lys	g aaa s Lys	a gat s Asp	gto Val 2235	l Leι	g agu 1 Sei	cto Lei	t too 1 Se	ggt Gly 2240	6720
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35	cgg ago Arg Ser	ttc Phe	atg Met 20	cgg Arg	ctc Leu	aac Asn	gac Asp	ctg Leu 25	tcg Ser	ggg Gly	gcc Ala	Gly	999 Gly 30	cgg Arg	ccg Pro	96
40	ggg ccg Gly Pro	ggg Gly 35	361	gca Ala	gaa Glu	aag Lys	gac Asp 40	ccg Pro	ggc Gly	agc Ser	gcg Ala	gac Asp 45	tcc Ser	gag Glu	gcg Ala	144
45	gag ggg Glu Gly 50		ccg Pro	tac Tyr	ccg Pro	gcg Ala 55	ctg Leu	gcc Ala	ccg Pro	gtg Val	gtt Val 60	ttc Phe	ttc Phe	tac Tyr	ttg Leu	192
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	ccc tgg Pro Trp	ttt Phe	gag Glu	cgc Arg 85	atc Ile	agc Ser	atg Met	ttg Leu	gtc Val 90	atc Ile	ctt Leu	ctc Leu	aac Asn	tgc Cys 95	gtg Val	288
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		130				•	135					140					
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10															agc Ser 175		528
70															att Ile		576
15															acg Thr		624
20															ttc Phe		672
25				_		-	-	-		-		_			aac Asn	-	720
30															ctg Leu 255		768
30															tgc Cys		816
35															acg Thr		864
40	cgc Arg	ggg Gly 290	gac Asp	ggg Gly	ggc Gly	ggt Gly	ggc Gly 295	cca Pro	cct Pro	tgc Cys	ggt Gly	ctg Leu 300	gac Asp	tat Tyr	gag Glu	gcc Ala	912
45															tac Tyr		960
50	acc Thr	aac Asn	tgc Cys	tca Ser	gcg Ala 325	ggg Gly	gag Glu	Cac	aac Asn	ccc Pro 330	ttc Phe	aag Lys	ggc Gly	gcc Ala	atc Ile 335	aac Asn	1008
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60			Asn					Ile					Val		tcc Ser		1152
															tca Ser		1200

	38	5				39	0				39:	Ē				400	
5	acc Th:	c aa r Ly	g ca s Gì	g og n Ar	g gaa g Gl: 40:	3 9 0 1	c cad r Glr	g cto n Lei	g ato u Met	g egg : Arg 410	; Git	g ca: u Gl:	g og: n Ard	g ya	g cg l Are 41	g tto g Phe 5	1248
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	ggg Gly	gac Asp	acc Thr	ctg	cca Pro	gac Asp	cgg Arg	aag	aat Asn	ttt Phe	gac Asp	tcc Ser	ttg Leu	ctc Leu	tgg Trp	gcc	2736

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	att Ile 945	gco Ala	c cto	c ato u Me	g aco t Thr	Phe 950	ggc Gly	aac Asn	tac Tyr	gtg Val	ctc Leu 955	Phe	aat Asr	tto Lei	g cto 1 Let	g gtc 2 Val 960	2880
15	gcc Ala	att Il∈	cto Lev	g gto u Val	g gag l Glu 965	· Oxy	ttc Phe	cag Gln	gcg Ala	gag Glu 970	СТУ	gat Asp	gcc Ala	aac Asr	aaq Lys	tcc Ser	2928
20	gaa Glu	tca Ser	gaç Glu	980	cp	ttc Phe	ttc Phe	tca Ser	ccc Pro 985	ser	ctg Leu	gat Asp	ggt Gly	gat Asp 990	61?	gac Asp	- 2976
25	agg Arg	aag Lys	aag Lys 995		ttg Leu	gcc Ala	neu	gtg Val 1000	tcc Ser	ctg Leu	gga Gly	Glu	cac His 1005	ccg Pro	gaç Glu	ctg Leu	3024
30	_	aag Lys 1010		Ctg Leu	ctg Leu	LIO	cct Pro L015	ctc Leu	atc Ile	atc Ile	His	acg Thr 1020	gcc Ala	gcc Ala	aca Thr	ccc Pro	3072
	atg Met 1025	tcg Ser	ctg Leu	ccc Pro	- y 3	agc Ser 1030	acc Thr	agc Ser	acg Thr	CTÀ	ctg Leu 1035	ggc Gly	gag Glu	gcg Ala	Leu	ggc Gly 1040	3120
35	cct Pro	gcg Ala	tcg Ser	9	cgc Arg 1045	acc Thr	agc Ser	agc Ser	ser	ggg Gly L050	tcg Ser	gca Ala	gag Glu	Pro	ggg Gly 1055	gcg Ala	3168
40	gcc Ala	cac His		atg Met 1060	aag Lys	tca Ser	ccg Pro	FIO	agc Ser 065	gcc Ala	cgc Arg	agc Ser	Ser	ccg Pro .070	cac His	agc Ser	3216
45	ccc Pro		agc Ser 1075	gct Ala	gca Ala	agc Ser	Jer	tgg Trp .080	acc Thr	agc Ser	agg Arg	Arg	tcc Ser 085	aġc Ser	cgg Arg	aac Asn	3264
50		ctc Leu 090	ggc Gly	cgt Arg	gca Ala	ccc Pro 1	agc Ser 095	ctg Leu	aag Lys	cgg Arg	Arg .	agc Ser 100	cca Pro	agt Ser	gga Gly	gag Glu	3312
	cgg Arg 1105		tcc Ser	ctg Leu	ac u	tcg Ser 110	gga Gly	gaa Glu	ggc Gly	GIN	gag Glu : 115	agc Ser	cag Gln	gat Asp	Glu	gag Glu 120	3360
55	gag Glu	agc Ser	tca Ser		gag Glu 125	gag (Glu <i>i</i>	cgg Arg	gcc Ala	ser	cct Pro 130	gcg (Ala (ggc Gly	agt Ser	Asp	cat His 135	cgc Arg	3408
60	cac His	agg Arg		tcc Ser 140	ctg Leu	gag o Glu <i>l</i>	egg Arg	GIU,	gcc Ala :	aag . Lys :	agt t Ser S	cc : Ser :	Phe .	gac Asp 150	ctg Leu	çca Pro	3456
	gac a Asp :	aca Thr	ctg Leu	cag Gln	gtg Val	cca q Pro (ggg (ctg (Leu 1	cat (His /	cgc a	act o	gcc a Ala S	agt (Ser (ggc Gly	cga Arg	ggg Gly	3504

	1155		1160	1165	
5		Glu His Gla		ggc aag tcg gct : Gly Lys Ser Ala : 1180	
10	ctg gcc cgg Leu Ala Arg 1185	gcc ctg cgg Ala Leu Arg 1190	cct gat gac Pro Asp Asp	ccc cca ctg gat of Pro Pro Leu Asp of 1195	ggg gat gac 3600 Gly Asp Asp 1200
70			Leu Ser Lys	ggg gaa cgg gtc : Gly Glu Arg Val : 1210	
15	Ile Arg Ala			ctc gag cga gac Leu Glu Arg Asp	
20		Phe Pro Pro		ttc cgc ctc ctg Phe Arg Leu Leu 1245	
25		His Lys Met		gtg gtc ctt gtc . Val Val Leu Val 1260	
<i>30</i> -				cgc ccc aaa att Arg Pro Lys Ile 1275	
50			Leu Thr Leu	tcc aat tac atc Ser Asn Tyr Ile 1290	
35	Val Phe Leu			gtg gtg gca ctg Val Val Ala Leu 1	
40		Gln Ala Tyr		agt tgg aac gtg Ser Trp Asn Val 1325	
45		Leu Ile Ser		att ctg gtg tcc Ile Leu Val Ser 1340	
50				ctg agg gtg ctg Leu Arg Val Leu 1355	
50			Arg Val Ile	agc cgg gcg cag Ser Arg Ala Gln 1370	
55				ctg aaa ccc atc Leu Lys Pro Ile 1	
60	gta gtc atc Val Val Ile 1395	Cys Cys Ala	ttc ttc atc Phe Phe Ile 1400	att ttc ggc atc Ile Phe Gly Ile 1405	ttg ggg gtg 4224 Leu Gly Val
	cag ctc ttc Gln Leu Phe	aaa ggg aag Lys Gly Lys	ttt ttc gtg Phe Phe Val	tgc cag ggc gag Cys Gln Gly Glu	gat acc agg 4272 Asp Thr Arg

	1410	141	5	1420	
5	aac atc acc Asn Ile Thr 1425	aat aaa tog ga Asn Lys Ser As 1430	c tgt gcc gag gc p Cys Ala Glu Al 143	c agt tac cgg tgg gt a Ser Tyr Arg Trp Va 5 144	11
10	cgg cac aag Arg His Lys	tac aac ttt ga Tyr Asn Phe As 1445	c aac ctt ggc ca p Asn Leu Gly Gl: 1450	g gcc ctg atg tcc ct n Ala Leu Met Ser Le 1455	g 4368 eu
	the var red	gcc tcc aag ga Ala Ser Lys As 1460	t ggt tgg gtg gaa p Gly Trp Val Asp 1465	c atc atg tac gat gg p Ile Met Tyr Asp Gl 1470	g 4416 Y
15	ctg gat gct Leu Asp Ala 1475	gtg ggc gtg ga Val Gly Val As	c cag cag ccc ato p Gln Gln Pro Ile 1480	c atg aac cac aac cc e Met Asn His Asn Pr 1485	c 4464 o
20	tgg atg ctg Trp Met Leu 1490	ctg tac ttc at Leu Tyr Phe Il 149	e Ser Phe Leu Lei	c att gtg gcc ttc tt u Ile Val Ala Phe Ph 1500	t 4512 e
25	gtc ctg aac Val Leu Asn 1505	atg ttt gtg gg Met Phe Val Gl 1510	t gtg gtg gtg gag y Val Val Val Glu 1515	g aac ttc cac aag tg u Asn Phe His Lys Cy 5 152	s
30	cgg cag cac Arg Gln His	cag gag gaa ga Gln Glu Glu Gl 1525	g gag gcc cgg cgc u Glu Ala Arg Arc 1530	g cgg gag gag aag cg g Arg Glu Glu Lys Ar 1535	c 4608 g
	Leu Arg Arg	ctg gag aaa aa Leu Glu Lys Ly: 1540	g aga agg aat cta s Arg Arg Asn Lei 1545	a atg ctg gac gat gt u Met Leu Asp Asp Va 1550	a 4656 1 -
35	att gct tcc Ile Ala Ser 1555	ggc agc tca gcc Gly Ser Ser Ala	c agc gct gcg tca a Ser Ala Ala Ser 1560	a gaa gcc cag tgc aa r Glu Ala Gln Cys Ly 1565 .	a 4704 s
40	cct tac tac Pro Tyr Tyr 1570	tcc gac tac tcc Ser Asp Tyr Ser 1575	r Arg Phe Arg Leu	c ctc gtc cac cac tto Leu Val His His Le 1580	g 4752 u
45	tgc acc agc Cys Thr Ser 1585	cac tac ctg gad His Tyr Leu Asp 1590	c ctc ttc atc aca c Leu Phe Ile Thr 1595	a ggt gtc atc ggg ctc r Gly Val Ile Gly Len 5 1600	ū.
50	aac gtg gtc Asn Val Val	acc atg gcc atg Thr Met Ala Met 1605	g gag cac tac cag t Glu His Tyr Gln 1610	g cag ccc cag att cto n Gln Pro Gln Ile Leo 1615	g 4848 u
	Asp Glu Ala	ctg aag atc tgo Leu Lys Ile Cys 1620	c aac tac atc ttc s Asn Tyr Ile Phe 1625	e act gtc atc ttt gtc e Thr Val Ile Phe Val 1630	= ⁴⁸⁹⁶
<i>55</i>	ttg gag tca Leu Glu Ser 1635	gtt ttc aaa ctt Val Phe Lys Lei	gtg gcc ttt ggt Val Ala Phe Gly 1640	ttc cgt cgg ttc ttc y Phe Arg Arg Phe Phe 1645	2 4944 e
60	cag gac agg Gln Asp Arg 1650	tgg aac cag ctg Trp Asn Gln Let 1655	ı Asp Leu Ala Ile	gtg ctg ctg tcc atc Val Leu Leu Ser Ile 1660	4992
	atg ggc atc Met Gly Ile	acg ctg gag gaa Thr Leu Glu Glu	a atc gag gtc aac 1 Ile Glu Val Asn	c gcc tcg ctg ccc ato n Ala Ser Leu Pro Ile	5040

17

	1665	1	.670		1675	1680	
ŝ	aac ccc a Asn Pro T	cc atc atc hr lle lle 1685	cgc atc a	atg agg gt Met Arg Va 169	g ctg cgc att Leu Arg Ile O	gcc cga gtg Ala Arg Val 1695	5386
10	ctg aag c Leu Lys L	tg ctg aag eu Leu Lys 1700	atg gct (Met Ala '	gtg ggc at Val Gly Me 1705	g egg geg etg et Arg Ala Lev	g ctg gac acg 1 Leu Asp Thr 1710	,5136
10	Val Met G	ag gcc ctg ln Ala Leu 15	Pro Gln '	gtg ggg aa Val Gly As 720	ic ctg gga ctt in Leu Gly Leu 1725	Leu Phe Met	5184
15	ttg ttg t Leu Leu P 1730	tt ttc atc he Phe Ile	ttt gca o Phe Ala i 1735	gct ctg gg Ala Leu Gl	gc gtg gag cto y Val Glu Lev 1740	ttt gga gac 1 Phe Gly Asp	5232
20	ctg gag t Leu Glu C 1745	ys Asp Glu	aca cac o Thr His 1 750	ccc tgt ga Pro Cys Gl	g ggc ctg ggc u Gly Leu Gly 1755	c cgt cat gcc / Arg His Ala 1760	5280
25	acc ttt c Thr Phe A	gg aac ttt rg Asn Phe 1765	ggc atg o Gly Met A	gcc ttc ct Ala Phe Le 177	a acc ctc ttc u Thr Leu Phe	c cga gtc tcc Arg Val Ser 1775	5328
30	aca ggt g Thr Gly A	ac aat tgg sp Asn Trp 1780	aat ggc a Asn Gly :	att atg aa Ile Met Ly 1785	g gac acc cto s Asp Thr Leu	c cgg gac tgt n Arg Asp Cys 1790	5376
30	Asp Gln G	ag tcc acc lu Ser Thr 95	Cys Tyr A	aac acg gt Asn Thr Va 800	c atc tcg cct l lle Sar Pro 1805	o Ile Tyr Phe	5424
35	gtg tcc t Val Ser P 1810	tc gtg ctg he Val Leu	acg gcc (Thr Ala (1815	cag ttc gt Gln Phe Va	g cta gtc aac l Leu Val Asr 1820	gtg gtg atc Nal Val Ile	5472
40	gcc gtg c Ala Val L 1825	eu Met Lys	cac ctg o His Leu (830	gag gag ag Glu Glu Se	c aac aag gaq r Asn Lys Gli 1835	g gcc aag gag n Ala Lys Glu n 1840	5520
45	gag gcc g Glu Ala G	ag cta gag lu Leu Glu 1845	gct gag (Ala Glu)	ctg gag ct Leu Glu Le 185	g gag atg aag u Glu Met Lys O	acc ctc agc Thr Leu Ser 1855	5568
50	ccc cag c Pro Gln P	cc cac tcg ro His Ser 1860	cca ctg (Pro Leu (ggc agc cc Gly Ser Pr 1865	c ttc ctc tgc o Phe Leu Trr	cct ggg gtc Pro Gly Val	561,6
50	Glu Gly P	cc gac agc ro Asp Ser 75	Pro Asp S	agc ccc aa Ser Pro Ly 880	g cct ggg gct s Pro Gly Ala 1885	Leu His Pro	. 5664
<i>55</i> .	gcg gcc c Ala Ala H 1890	ac gcg aga is Ala Arg	tca gcc (Ser Ala (1895	tcc cac tt Ser His Ph	t tcc ctg gag e Ser Leu Gli 1900	g cac ccc acg n His Pro Thr	5712
60	atg cag c Met Gln P 1905	ro His Pro	acg gag o Thr Glu 1 910	ctg cca gg Leu Pro Gl	a cca gac tta y Pro Asp Let 1915	a ctg act gtg 1 Leu Thr Val 1920	5760
	cgg aag t Arg Lys S	ct ggg gtc er Gly Val	agc cga a Ser Arg 1	acg cac to Thr His Se	t ctg ccc aat r Leu Pro Asr	gac agc tac Asp Ser Tyr	5808

				1925	ı				1930					1935	:	
5	atg tg: Met Cy:	i ogg s Arg	cat His 1940	ету	agc Ser	act	gco Ala	gag Glu 1945	Gly	ccc Pro	ctg Leu	gga Gly	cac His	Arç	ggc Gly	5856
10	tgg ggg Trp Gly	g ctc / Leu 1955	Pro	aaa Lys	gct Ala	Gin	tca Ser 1960	Gly	tcc Ser	gtc Val	Leu	tcc Ser 1965	Val	cac His	tcc Ser	5904
	cag cca Gln Pro 1970	Ala	gat Asp	acc Thr	Ser	tac Tyr 1975	atc Ile	ctg Leu	cag Gln	Leu	ccc Pro 1980	aaa Lys	gat Asp	gca Ala	cct Pro	5952
15	cat cto His Leu 1985	g ctc Leu	cag Gln	Pro	cac His 1990	agc Ser	gcc Ala	cca Pro	Thr	tgg Trp 1995	ggc Gly	acc Thr	atc Ile	ccc Pro	aaa Lys 2000	6000
20	ctg ccc Leu Pro	cca Pro	PIO	gga Gly 2005	egc Arg	tcc Ser	cct Pro	Leu	gct Ala 2010	cag Gln	agg Arg	cca Pro	Leu	agg Arg 2015	cgc Arg	.6048
25	cag gca Gln Ala	Ата	ata Ile 2020	agg Arg	act Thr	gac Asp	Ser	ttg Leu 2025	gac Asp	gtt Val	cag Gln	Gly	ctg Leu 2030	ggc Gly	agc Ser	6096
30	cgg gaa Arg Glu	gac Asp 2035	ctg Leu	ctg .Leu	.gca Ala	Glu	gtg Val 2040	agt Ser	ggg Gly	ccc Pro	Ser	ccg Pro 2045	ccc Pro	ctg Leu	gcc Ala	6144
	cgg gcc Arg Ala 2050	TAT	tct Ser	ttc Phe	Trp	ggc Gly 2055	cag Gln	tca Ser	agt Ser	Thr	cag Gln 2060	gca Ala	cag Gln	cag Gln	cac His	6192
35	tcc cgc Ser Arg 2065	agc Ser	cac His	Ser	aag Lys 2070	atc Ile	tcc Ser	aag Lys	His	atg Met 2075	acc Thr	ccg Pro	cca Pro	Ala	cct Pro 2080	6240
40	tgc cca Cys Pro	ggc Gly	Pro	gaa Glu 2085	ccc Pro	aac Asn	tgg Trp	Gly	aag Lys 2090	ggc Gly	cct Pro	cca Pro	Glu	acc Thr 2095	aga Arg	6288
45	agc agc Ser Ser	rea	gag Glu 2100	ttg Leu	gac Asp	acg Thr	GIU	ctg Leu 2105	agc Ser	tgg Trp	att Ile	Ser	gga Gly 2110	gac Asp	ctc Leu	6336
50	ctg ccc Leu Pro	cct Pro 2115	ggc Gly	ggc Gly	cag Gln	GLu	gag Glu 120	ccc Pro	cca Pro	tcc Ser	Pro	cgg Arg 125	gac Asp	ctg Leu	aag Lys	6384
	aag tgc Lys Cys 2130	tac Tyr	agc Ser	gtg Val	Glu	gcc Ala 2135	cag Gln	agc Ser	tgc Cys	Gln	cgc Arg 140	cgg Arg	cct Pro	acg Thr	tcc Ser	6432
55	tgg ctg Trp Leu 2145	gat Asp	gag Glu	Gin	agg Arg 150	aga Arg	cac His	tct Ser	Ile	gcc Ala 155	gtc Val	agc Ser	tgc Cys	Leu	gac Asp 2160	6480
60	agc ggc Ser Gly	tcc ³ Ser	GTU	ccc Pro	cac His	ctg Leu	ggc Gly	Thr	gac Asp 170	ccc Pro	tct. Ser	aac Asn	Leu	ggg Gly 175	ggc Gly	. 6528
	cag cct Gln Pro	ctt Leu	ggg Gly	GJ À āāā	cct Pro	Gly ggg	agc Ser	cgg Arg	ccc Pro	aag Lys	aaa Lys	aaa Lys	ctc Leu	agc Ser	cċg Pro	6576

	2130		2135		2190	
5	cot agt atc acc Pro Ser Ile Thr 2195	Ile Asp Pro		Ser Gin Gly		
10	ccc ago cot ggt Pro Ser Pro Gly 2210					
10	aag gat ccc ttg Lys Asp Pro Leu 2225	ged tot ggd Ala Ser Gly 2230	occ cot o Pro Pro A	gac agc atg Asp Ser Met 2235	Ala Ala Ser	ccc 6720 9ro 2240
15	tcc cca aag aaa Ser Pro Lys Lys		Ser Leu S			
20	gca gac ctg gac Ala Asp Leu Asp 2260	Pro				6783
25	<210> 3 <211> 6804 <212> DNA <213> Homo sapi	ens		·		
30	<220> <221> CDS <222> (1)(680	. 4)				
35	<400> 3 atg gac gag gag Met Asp Glu Glu 1	g gag gat gga B Glu Asp Gly 5	gcg ggc g Ala Gly A	gcc gag gag Ala Glu Glu 10	tcg gga cag Ser Gly Gln 15	ccc 48 Pro
40	cgg agc ttc atg Arg Ser Phe Met 20	. Arg Leu Asn	gac ctg t Asp Leu S 25	tog ggg gcc Ser Gly Ala	gġg ggg cgg Gly Gly Arg 30	ccg 96 Pro .
45	ggg ccg ggg tca Gly Pro Gly Ser 35	gca gaa aag Ala Glu Lys	gac ccg c Asp Pro 0 40	ggc agc gcg Gly Ser Ala	gac too gag Asp Ser Glu 45	gcg 144 Ala
43	gag ggg ctg ccg Glu Gly Leu Pro 50	g tac cog gog o Tyr Pro Ala 55	ctg gcc d Leu Ala B	ccg gtg gtt Pro Val Val 60	tto tto tac Phe Phe Tyr	ttg 192 Leu
50	agc cag gac agc Ser Gln Asp Ser 65	c cgc ccg cgg Arg Pro Arg 70	agc tgg t Ser Trp (tgt ctc cgc Cys Leu Arg 75	acg gtc tgt Thr Val Cys	aac 240 Asn 80
<i>55</i>	ccc tgg ttt gag Pro Trp Phe Glu	g cgc atc agc 1 Arg Ile Ser 85	atg ttg (Met Leu \	gtc atc ctt Val Ile Leu 90	ctc aac tgc Leu Asn Cys 95	Val
60	acc ctg ggc atc Thr Leu Gly Met 100	Phe Arg Pro	tgc gag d Cys Glu # 105	gac atc gcc Asp Ile Ala	tgt gad tod Cys Asp Ser 110	cag 336 Gln
	cgc tgc cgg ato Arg Cys Arg Ile 115	ctg cag goo Leu Gln Ala	ttt gat o Phe Asp i 120	gac ttc atc Asp Pne Ile	tit god tid Phe Ala Phe 125	: tit 384 : Phe

5	gco Ala	gtg Val 130	13 L U	ratç Met	geg Val	gtg Val	aag Lys 135	Met	gtg Val	god Ala	ttg Leu	ggc Gly 140	Ile	t t t Phe	gge Gly	aaa Lys	432
	aag Lys 145	∪ys	tac Tyr	: ctg Leu	gga Gly	gac Asp 150	Thr	tgg Trp	aac Asn	cgg Arg	ctt Leu 155	Asp	ttt Phe	tto Phe	ato Ile	gtc Val 160	480
10	ato Ile	gca Ala	G1 A	atg Met	ctg Leu 165	gag Glu	tác Tyr	tog Ser	ctg Leu	gac Asp 170	Leu	cag Gln	aac Asn	gto Val	ago Ser 175	ttc Phe	528
15	tca Ser	gct Ala	gtc Val	agg Arg 180	Thr	gtc Val	cgt Arg	gtg Val	ctg Leu 185	cga Arg	ccg Pro	ctc Leu	agg Arg	gcc Ala 190	att Ile	aac Asn	576
20	egg Arg	gtg Val	ccc Pro 195	agc Ser	atg Met	cgc Arg	atc Ile	ctt Leu 200	gtc Val	acg Thr	ttg Leu	ctg Leu	ctg Leu 205	gat Asp	acg Thr	ctg Leu	624
25	ccc Pro	atg Met 210	ctg Leu	Gly	aac Asn	gtc Val	ctg Leu 215	ctg Leu	ctc Leu	tgc Cys	ttc Pne	ttc Phe 220	gtc Val	ttc Phe	ttc Phe	atc Ile	672
	ttc Phe 225	ggc Gly	atc Ile	gtc Val	ggc Gly	gtc Val 230	cag Gln	ctg Leu	tgg Trp	gca Ala	999 Gly 235	ctg Leu	ctt Leu	cgg Arg	aac Asn	cga Arg 240	720
30	tgc Cys	ttc Phe	cta Leu	cct Pro	gag Glu 245	aat Asn	ttc Phe	agc Ser	ctc Leu	ccc Pro 250	ctg Leu	agc Ser	gtg Val	gac Asp	ctg Leu 255	gag Glu	768
35	cgc Arg	tat Tyr	tac Tyr	cag Gln 260	aca Thr	gag Glu	aac Asn	gag Glu	gat Asp 265	gag Glu	agc Ser	ccc Pro	ttc Phe	atc Ile 270	tgc Cys	tcc Ser	816
40	cag Gln	cca Pro	cgc Arg 275	gag Glu	aac Asn	ggc Gly	atg Met	cgg Arg 280	tcc Ser	tgc Cys	aga Arg	agc Ser	gtg Val 285	ccc Pro	acg Thr	ctg Leu	864
<i>45</i>	cgc Arg	ggg Gly 290	gac Asp	Gly	ggc Gly	ggt Gly	ggc Gly 295	cca Pro	cct Pro	tgc Cys	ggt Gly	ctg Leu 300	gac Asp	tat Tyr	gag Glu	gcc Ala	912
	tac Tyr 305	aac Asn	agc Ser	tcc Ser	agc Ser	aac Asn 310	acc Thr	acc Thr	tgt Cys	gtc Val	aac Asn 315	tgg Trp	aac Asn	cag Gln	tac Tyr	tac Tyr 320	960
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<i>55</i>	ttt Phe	gac Asp	aac Asn	att Ile 340	ggc Gly	tat Tyr	gcc Ala	tgg Trp	atc Ile 345	gcc Ala	atc Ile	ttc Phe	cag Gln	gtc Val 350	atc Ile	acg Thr	1056
60	ctg Leu	gag Glu	ggc Gly 355	tgg Trp	gtc Val	gac Asp	atc Ile	atg Met 360	tac Tyr	ttt Phe	gtg Val	atg Met	gat Asp 365	gct Ala	cat His	tc: Ser	1104
	ttc Phe	tac Tyr 370	aat Asn	ttc Phe	atc Ile	Tyr	ttc Phe 375	acc Ile	ctc Leu	ctc Leu	Ile	atc Ile 380	gtg Val	ggc Gly	tcc Ser	tto Phe	1152

ĵ.	ttc Phe 385	atg Met	atc Ile	aac Asn	otg Leu	tgc Cys 390	Ctg Leu	gig Val	gtg Val	att	gcc Ala 395	acg Thr	cag Gln	tts Phe	tca Ser	gag Glu 400	1200
J	açc Thr	aag Lys	cag Gln	cgg Arg	gaa Glu 405	agc Ser	cag Gln	ctg Leu	alg Met	ogg Arg 410	gag Glu	cag Gln	ogt Arg	g:g 7a1	ogg Arg 415	ttc Phe	1248
10	ctg Leu	toc Ser	aac Asn	gcc Ala 420	agc Ser	acc Thr	ctg Leu	gct Ala	agc Ser 425	ttc Phe	tct Ser	gag Glu	ees Pro	ggc Gly 430	Ser	tgc Cys	1296
15	tat Tyr	gag Glu	gag Glu 435	ctg Leu	ctc Leu	aag Lys	tac Tyr	ctg Leu 440	gtg Val	Tyr	atc Ile	ctt Leu	ogt Arg 445	aag Lys	gca Ala	gcc Ala	1344
20	cgc Arg	agg Arg 450	ctg Leu	gct Ala	cag Gln	gtc Val	tct Ser 455	cgg Arg	gca Ala	gca Ala	ggt Gly	gtg Val 460	cgg Arg	gtt Val	ggg Gly	ctg Leu	1392
25	ctc Leu 465	agc Ser	agc Ser	cca Pro	gca Ala	ccc Pro 470	ctc Leu	Gly ggg	ÖŢĀ āā≎	cag Gln	gag Glu 475	acc Thr	cag Gln	ccc 9ro	agc Ser	agc Ser 480	1440
23	agc Ser	tgc Cys	tct Ser	cgc Arg	tcc Ser 485	cac His	cgc Arg	cgc Arg	cta Leu	tcc Ser 490	gtc Val	cac His	cac His	ctg Leu	gtg Val 495	cac His	1488
30	cac His	cac His	cac His	cac His 500	cat His	cac His	cac His	cac His	tac Tyr 505	cac His	ctg Leu	ggc Gly	aat Asn	ggg Gly 510	acg Thr	ctc Leu	1536
35	agg Arg	gcc Ala	ccc Pro 515	cgg Arg	gcc Ala	agc Ser	ccg Pro	gag Glu 520	atc Ile	cag Gln	gac Asp	agg Arg	gat Asp 525	gcc Ala	aat Asn	ggg Gly	1584
40	tcc Ser	cgc Arg 530	cgg Arg	ctc Leu	atg Met	ctg Leu	cca Pro 535	cca Pro	ccc Pro	tcg Ser	acg Thr	cct Pro 540	gcc Ala	ctc Leu	tcc Ser	G] À Gàà	1632
45	gcc Ala 545	ccc Pro	cct Pro	ggt Gly	ggc Gly	gca Ala 550	gag Glu	tct Ser	gtg Val	cac His	agc Ser 555	ttc Phe	tac Tyr	cat His	gcc Ala	gac Asp 560	1680
43	tgc Cys	cac His	tta Leu	gag Glu	cca Pro 565	gtc Val	cgc Arg	tgc Cys	cag Gln	gcg Ala 570	ccc Pro	Pro	ccc Pro	agg Arg	tcc Ser 575	Pro	1728
50	tct Ser	gag Glu	gca Ala	tcc Ser 580	Gly	agg Arg	act Thr	gtg Val	ggc Gly 585	agc Ser	ggg Gly	aag Lys	gtg Val	tat Tyr 590	ccc Pro	acc Thr	1776
<i>55</i>	gtg Val	cac His	acc Thr 595	Ser	cct Pro	cca Pro	510 CCâ	gag Glu 600	acg Thr	ctg Leu	aag Lys	gag Glu	aag Lys 605	gca Ala	cta Leu	gta ·Val	1824
60	gag Glu	gtg Val 610	Ala	gcc Ala	agc Ser	tct Ser	999 615	ccc Pro	cca Pro	acc Thr	ctc Leu	acc Thr 620	Ser	ctc Leu	aac Asn	atc Ile	1872
	cca Pro 625	Pro	Gly	ccc	tac Tyr	agc Ser 630	Ser	atg Met	cac His	aag Lys	ctg Leu 635	Leu	gag Glu	aca Thr	cag Gln	agt Ser 640	1920

Ī	aca Thr	ggt Gly	gcc Ala	t go Cys	caa Gln 645	agc Ser	tat Ser	tgo Cys	aag Lys	atc Ile 650	Ser	age Ser	Bro GGI	tgo Cys	ttg Leu 655	aaa Lys	1963
	gca Ala	gac Asp	agt Ser	gga Gly 660	gee Ala	tgt Cys	ggt Gly	pro	gac Asp 665	agc Ser	tgc Cys	Sto	tac Tyr	tgt Cys 670	Ala	ogg Arg	2016
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35	gag Glu	gag Glu 770	ctt Leu	acc Thr	aac Asn	gcc Ala	cta Leu 775	gaa Glu	atc Ile	agc Ser	aac Asn	atc Ile 780	gtc Val	ttc Phe	acc Thr	agc Ser	2352
40	ctc Leu 785	ttt Phe	gcc Ala	ctg Leu	gag Glu	atg Met 790	ctg Leu	ctg Leu	aag Lys	ctg Leu	ctt Leu 795	gtg Val	tat Tyr	ggt Gly	ccc Pro	ttt Phe 800	2400
45	ggc Gly	tac Tyr	átc Ile	aag Lys	aat Asn 805	ccc Pro	tac Tyr	aac Asn	atc Ile	ttc Phe 810	gat Asp	ggt Gly	gtc Val	att Ile	gtg Val 815	gtc Val	2448
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	atc Ile	ctg Leu	ggc Gly	atg Met	cat His 835	ctc Leu	ttc Phe	gge Gly	tgc Cys	aag Lys 890	ttt Phe	gcc Ala	tct Ser	gag Glu	892 Yzá cáá	gat Asp	2688

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															aaa Lys		2784
10															tat Tyr		2832
15	att Ile 945	gcc Ala	ctc Leu	atg Met	acc Thr	tto Phe 950	ggc Gly	aac Asn	tac Tyr	gtg Val	ctc Leu 955	ttc Phe	aat Asn	ttg Leu	ctg Leu	gtc Val 960	2830
20	gcc Ala	att Ile	.ctg Leu	gtg Val	gaş Glu 965	gg: Gly	ttc Phe	cag Gln	gcg Ala	gag Glu 970	gga Gly	gat Asp	gc: Ala	aac Asn	aag Lys 975	tcc Ser	2928
25															Gly		2976
23	agg Arg	aag Lys	aag Lys 995	tgc Cys	ttg Leu	gcc Ala	Leu	gtg Val 1000	tcc Ser	ctg Leu	gga Gly	Glu	cac His 1005	ccg Pro	gag Glu	ctg Leu	3024
30	Arg	aag Lys L010	agc Ser	ctg Leu	ctg Leu	Pro	cct Pro LO15	ctc Leu	atc Ile	atc Ile	His	acg Thr LO20	gcc Ala	gcc Ala	aca Thr	ccc Pro	3072
35	atg Met 102	Ser	ctg Leu	ccc Pro	Lys	agc Ser 1030	acc Thr	agc Ser	acg Thr	Gly	ctg Leu 1035	ggc Gly	gag Glu	gcg Ala	ctg Leu	ggc Gly LO40	3120
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4 5	ttc c	Sly	gag Glu 315	cag Gln	gcg Ala	tac Tyr	Leu	egg Arg 320	agc Ser	agt Ser	tgg Trp	Asn	gtg Val 325	ctg Leu	gac Asp	Gly	3984
	ctg t Leu I	ttg Leu 330	gtg Val	ctc Leu	atc Ile	Ser	gtc Val .335	atc Ile	gac Asp	att Ile	Leu	gtg Val .340	tcc Ser	atg Met	gtc Val	tct Ser	4032
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55	cgg a Arg T	acc [.] Thr	ctg Leu	Arg	ccg Pro .365	ctc Leu	agg Arg	gtg Val	Ile	agc Ser 370	cgg Arg	gcg Ala	cag Gln	Gly	ctg Leu .375	aag Lys	4128
60	ctg ç Leu V	gtg /al	Val	gag Glu 380	acg Thr	ctg Leu	atg Met	Ser	tca Ser 385	CEg Leu	aaa Lys	ccc Pro	Ile	ggc Gly 390	aac Asn	att Ile	4176
	gta ç Val V	/al	atc Ile 395	tgc Cys	tgt Cys	gcc Ala	Phe	ttc Phe 400	atc Ile	att Ile	ttc Phe	Gly	atc Ile 405	ttg Leu	ej ř. aaa	gtg Val	4224

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10	ogg cac a	Lys Tyr					Leu Met S		÷363
15	tto gtt : Phe Val :			Asp Gly					4416
20	ctg gat o Leu Asp A					Ile Met			4464 ·
25	tgg atg (Trp Met 1 1490		Tyr Phe						4512
	gtc ctg a Val Leu i 1505	aac atg Asn Met	ttt gtg Phe Val 1510	ggt gtg Gly Val	Val Val	gag aac Glu Asn 515	ttc cac a Phe His I	aag tgt Lys Cys 1520	4560
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			Arg Phe				cag cig Glm Leu		4992

5	gcc att gtg ctg Ala Ile Val Let 1665	ctg too ato Leu Ser Ile 1670	Met Gly Ile	acg ctg gag gaa Thr Leu Glu Gl: 1675	a ato gag 5040 File Glu 1680
	gto aac goo tog Val Asn Ala Ser	ctg ccc atc Leu Pro Ile 1685	aar ccc acc Asn Pro Thr 1690	atc atc cgs atc	atş agg 5088 Met Arg 1695
10	gtg ctg cgc att Val Leu Arg Ile 1700	: Ala Arg Val	ctg aag ctg Leu Lys Leu 1705	ctg aag atg got Leu Lys Met Ala 1710	a Vai Gly
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20	aac ctg gga ctt Asn Leu Gly Leu 1730	ctc ttc atg Leu Phe Met 1735	ttg ttg ttt Leu Leu Phe	ttc atc ttt gca Phe Ile Phe Ala 1740	gct ctg 5232 Ala Leu
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	gag ggc ctg ggc Glu Gly Leu Gly	cgt cat gcc Arg His Ala 1765	acc ttt cgg Thr Phe Arg 1770	aac ttt ggc atg Asn Phe Gly Met	gcc ttc 5328 Ala Phe 1775
30	cta acc ctc ttc Leu Thr Leu Phe 1780	Arg Val Ser	aca ggt gac Thr Gly Asp 1785	aat tgg aat ggc Asn Trp Asn Gly 1790	Ile Met
35	aag gac acc ctc Lys Asp Thr Leu 1795	Arg Asp Cys	gac cag gag Asp Gln Glu 1800	tcc acc tgc tac Ser Thr Cys Tyr 1805	aac acg 5424 Asn Thr
40	gtc atc tcg cct Val Ile Ser Pro 1810	atc tac ttt Ile Tyr Phe 1815	gtg tcc ttc Val Ser Phe	gtg ctg acg gcc Val Leu Thr Ala 1820	cag ttc 5472 Gln Phe
4 5	gtg cta gtc aac Val Leu Val Asn 1825	gtg gtg atc Val Val Ile 1830	Ala Val Leu	atg aag cac ctg Met Lys His Leu 835	gag gag 5520 Glu Glu 1840
	Ser Asn Lys Glu	gcc aag gag Ala Lys Glu 1845	gag gcc gag Glu Ala Glu 1850	cta gag gct gag Leu Glu Ala Glu	ctg gag 5568 Leu Glu 1855
50	ctg gag atg aag Leu Glu Met Lys 1860	Thr Leu Ser	ccc cag ccc Pro Gln Pro 1865	cac tcg cca ctg His Ser Pro Leu 1870	Gly Ser
<i>55</i>	ccc ttc ctc tgg Pro Phe Leu Trp 1875	Pro Gly Val	gag ggc ccc Glu Gly Pro 1880	gac agc ccc gac Asp Ser Pro Asp 1885	age eec 5664 -Ser Pro
60	aag cet ggg get Lys Pro Gly Ala 1890	ctg cac cca Leu His Pro 1893	geg gee cac Ala Ala His	gcg aga tca gcc Ala Arg Ser Ala 1900	tcc cac 5712 Ser His
	ttt tcc ctg gag Phe Ser Leu Glu 1905	cac ccc acg His Pro Thr 1910	Met Gln Pro	cac ccc acg gag His Pro Thr Glu 915	ctg cca 5760 Leu Pro - 1920

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5	gga cca q Gly Pro A	Asp Leu	ctg act Leu Thr 1925	gig og Val Ar	g Lys	ser Gi 930	gg gto Ly Val	ago o Ser <i>l</i>	ga acç Arg Thr 1935	cac His	5808
	tot otg (Ser Leu i							Ser 7			5856
10	ggg ses a Gly Pro i	ctg gga Leu Gly 955	cac agg His Arg	ggc tg Gly Tr 196	p Gly	ctc co Leu Pr	co Lys	got d Ala (965	tag tca Bln Ser	ggc Gly	5904
15	tcc gtc : Ser Val i 1970	ttg tcc Leu Ser	get cac Val His	tcc ca Ser Gl 1975	g cca n Pro	gca ga Ala As	st acc sp Thr 1930	ago : Ser 1	ac atc Tyr Ile	ctg Leu	5952
20	cag ctt of Gln Leu ! 1985			Pro Hi			ln Pro		Ser Ala		6000
25	ace tgg (Thr Trp (Gly Thr	atc ccc Ile Pro 2005	aaa ct Lys Le	u Pro	cca co Pro Pr 2010	ca gga co Gly	ege t Arg S	Ser Pro 2015	ttg Leu	6048
	gct cag a Ala Gln a							Thr A			6096
30	gac gtt o Asp Val o				g Glu		eu Leu				6144
35	ggg ccc : Gly Pro : 2050	tcc ccg Ser Pro	ccc ctg Pro Leu	gcc cg Ala Ar 2055	g gcc g Ala	tac to Tyr Se	er Phe 2060	tgg (Trp (ggc cag Gly Gln	tca Ser	6192
40	agt acc Ser Thr (2065	cag gca Gln Ala	cag cag Gln Glr 2070	His Se	c cgc r Arg	agc ca Ser Hi 207	is Ser	aag a Lys :	Ile Ser	aag Lys 2080	6240
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	aag ggc Lys Gly	cct cca Pro Pro 2100	gag acc Glu Thr	aga aq Arg Se	gc agc er Ser 2105	tta ga Leu G	ag ttg lu Leu	Asp (acg gag Thr Glu 110	ctg Leu	6336
50	agc tgg Ser Trp 2				eu Pro		ly Gly				6384
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	atc gcc Ile Ala	Val.Ser			er Gly						6528

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,	ccc Pro	гÀг	aaa Lys 2195	Lys	ctc Leu	agc Ser	Pro	cct Pro 2200	Ser	atc Ile	acc Thr	ata Ile	gac Asp 2205	Pro	ccc Pro	gag Glu	6624
10	Ser	caa Gln 210	Gly	cct Pro	Arg	Thr	ccg Pro 2215	ccc Pro	agc Ser	cct Pro	Gly	atc Ile 2220	Суз	ct c Leu	egg Arg	agg Arg	6672
15	agg Arg 2225	gct Ala	ccg Pro	tcc Ser	Ser	gac Asp 2230	tcc Ser	aag Lys	gat Asp	Pro	ttg Leu 2235	gcc Ala	to: Ser	ggo	Pro	cct Pro 2240	6720
20	gac a	agc Ser	atg Met	Ala	gcc Ala 2245	tcg Ser	ccc Pro	tcc Ser	Pro	aag Lys 2250	aaa Lys	gat Asp	gtg Val	Leu	agt Ser 2255	ctc Leu	6768
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	cgg a Arg S	agc Ser	ttc Phe	atg Met 20	cgg Arg	ctc Leu	aac Asn	gac Asp	ctg Leu 25	tcg Ser	G]A aaa	gcc Ala	Gl ^v ggg	ggg Gly 30	cgg Arg	ccg Pro	96
<i>45</i>	Gly E	cg	999 Gly 35	tca Ser	gca Ala	gaa Glu	aag Lys	gac Asp 40	ccg Pro	ggc Gly	agc Ser	gcg Ala	gac Asp 45	tcc Ser	gag Glu	gcg Ala	144
50	gag g Glu G	20 21 A 33 A	ctg Leu	ccg Pro	tac Tyr	ccg Pro	gcg Ala 55	ctg Leu	gcc Ala	ccg Pro	gtg Val	gtt Val 60	ttc Phe	ttc Phe	tac Tyr	ttg Leu	192
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60	ccc t Pro T	rp gg	ttt Phe	gag Glu	cgc Arg 95	atc Ile	agc Ser	atg Met	ttg Leu	gtc Val 90	atc Ile	ctt Leu	ctc Leu	aac Asn	tgc Cys 95	gtg Val	288
	acc c Thr L	tg eu	ggc Gly	atg Met 100	tt: Phe	cgg Arg	cca Pro	tgc Cys	gag Glu 105	gac Asp	atc Ile	gcc Ala	tgt Cys	gac Asp	tcc Ser	cag Gln	336

	cgc Arg	tgc Cys	ogg Arg 115	ato Ile	ctg Leu	cag Gln	gcc Ala	Phe 120	gat Asp	dsY asc	ttc Phe	atc Ile	ttt Phe 125	god Ala	ttc Phe	ttt Phe	384
5	gcc Ala	gtg Val 130	gag Glu	atg Met	gig Val	gtg Val	aag Lys 135	atg Met	gtg Val	goo Ala	ttg Leu	ggc Gly 140	atc Ile	Phe	Gj. aaa	aaa Lys	÷32
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25	ccc Pro	atg Met 210	ctg Leu	ggc Gly	aac Asn	gtc Val	ctg Leu 215	ctg Leu	ctc Leu	tgc Cys	ttc Phe	ttc Phe 220	gtc Val	ttc Phe	ttc Phe	atc Ile	672
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40	cag Gln	cca Pro	cgc Arg 275	gag Glu	aac Asn	ggc Gly	atg Met	cgg Arg 280	tcc Ser	tgc Cys	aga Arg	agc Ser	gtg Val 285	ccc	acg Thr	ctg Leu	864
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	ttt Phe	gac Asp	aac Asn	att Ile 340	Gly	tat Tyr	gcc Ala	tgg Trp	atc Ile 345	gcc Ala	atc Ile	ttc Phe	cag Gln	gtc Val 350	atc Ile	acg Thr	1056
60	ctg Leu	gag Glu	ggc Gly 355	Trp	gtc Val	gac Asp	atc Ile	atg Met 360	Tyr	ttt Phe	gtg Val	atg Met	gat Asp 365	Ala	cat His	tcc Ser	1104

	tto Phe	ta: Ty:	- 22	t ti: n Phe	c ato	tac Tyr	2 tto 2 Ph = 375	; TT6	cto E Let	o oto 1 Let	c ato : Ile	ato = Ile 380	e Val	99 G1	c ts y Se	c ttc r Phe	1152
5	tto Phe 385	• •••	g ato	c aad e Asr	cto Leu	1 Ego 1 Cys 390	ret	g gtg . Val	; gtç . Val	, att	gcc Ala 395	Thi	g caq c Glr	tt: Ph	o to: e Se:	a gag Glu 400	1200
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25	ctc Leu 465	agc Ser	agc Ser	cca Pro	gca Ala	ccc Pro 470	ctc Leu	ggg Gly	Gly	cag Gln	gag Glu 475	acc Thr	cag Gln	ccc Pro	aşc Sər	agc Ser 480	1440
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31

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υυ	gtg Val 865	Ala	acc Thr	ttc Phe	tgc Cys	atg Met 870	Leu	stt Leu	atg Met	ctc Leu	ttc Phe 875	Įle	ttc Phe	atc Ile	tto Phe	agc Ser 880	2640 ·

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,,	gtc ttt Val Phe		a Ğlu I		Val					Leu				3936
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	ctt : Leu :	GJ A aaa	G] A G&&	Pro	999 Gly 165	agc Ser	cgg Arg	510 222	Lys	aaa Lys 170	aaa Lys	oso Leu	age Ser	Szo	ect Pro 175	agt Ser	6523
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40	<400 atg Met 1 cgt Arg ggg Gly gag Glu	agc Asp agc Ser ccg Pro ggg Gly 50	gag Glu ttc Phe ggg Gly 35 ctg Leu	gag Glu acg Thr 20 tcg Ser ccg Pro	gag Glu 5 cag Gln acg Thr	ctc Leu gaa Glu ccg Pro	aac Asn aag Lys gcg Ala 55	gac Asp gac Asp 40 cta Leu	ctg Leu 25 ccg Pro gcc Ala	Ala 10 tcc Ser ggc Gly ccg Pro	ggg Gly agc Ser gtg Val	gcc Ala gcg Ala gtt Val 60 cgc	ggg Gly gac Asp 45	ggc Gly 30 tcc Ser ttc Phe	Gln 15 cgg Arg gag Glu tac Tyr	cag Gln gcg Ala ttg Leu	96
40 45	<400 atg Met 1 cgt Arg ggg Gly gag Glu agc Ser 65	agc Asp agc Ser ccg Pro ggg Gly 50 cag	gag Glu ttc Phe ggg Gly 35 ctg Leu gac Asp	gag Glu acg Thr 20 tcg Ser ccg Pro	gag Glu 5 cag Gln acg Thr tac Tyr cgc Arg	Asp ctc Leu gaa Glu ccg Pro ccg Pro	aac Asn aag Lys gcg Ala 55 cgg Arg	gac Asp gac Asp 40 cta Leu agc ser	ctg Leu 25 ccg Pro gcc Ala	Ala 10 tcc Ser ggc Gly ccg Pro	ggg Gly agc Ser gtg Val ctc Leu 75 att Ile	gcc Ala gcg Ala gtt Val 60 cgc Arg	ggg Gly gac Asp 45 ttc Phe acg Thr	ggc Gly 30 tcc Ser ttc Phe gtc Val	Gln 15 cgg Arg gag Glu tac Tyr tgt Cys	cag Gln gcg Ala ttg Leu aac Asn 80 gtg Vai	96
40 45 50	<pre><400 atg Met 1 cgt Arg ggg Gly gag Glu agc Ser 65 ccg Pro act</pre>	agc Asp agc Ser ccg Pro ggg 50 cagn tgg Trp ctg	gag Glu ttc Phe ggg 35 ctg Leu gac Phe	gag Glu acg Thr 20 tcg Ser ccg Pro agcr gagu	gag Glu 5 cag Gln acg Thr tac Tyr cgc Arg cga Arg	Asp ctc Leu gaa Glu ccg Pro ccg Pro 70 gtc Val	aac Asn aag Lys gcg Ala 55 cgg Arg agt Ser ccg	gac Asp gac Asp 40 cta Leu agc ser atgt	ctg Leu 25 ccg Pro gcc Ala tgg Trp	Ala 10 tcc Ser ggc Gly ccg Pro tgt Cys gtc Val 90 gac	ggg Gly agc Ser gtg Val ctc Leu 75 att	gcc Ala gcg Ala gtt Val 60 cgc Arg	ggg Gly gac Asp 45 ttc Phe acg Thr ctc Leu tgt	ggc Gly 30 tcc Ser ttc Phe gtc Val	Gln 15 cgg Arg gag Glu tac Tyr tgt Cys 95 tcs Ser	cag Gln gcg Ala ttg Leu aac Asn 80 gtg Vai	96 144 192 240

			115	5				120)				125	5			
5	got Ala	gtq Val	الملادا	atç Met	g gtg Val	gtg Val	aaq Lys 135	Met	gto Val	g gcc Ala	tto Lev	9990 : Gly 140	Ile	ttt Phe	: ggg	aag Lys	432
10	aaa Lys 145	Cys	tac Tyr	ctg Leu	gga Gly	gac Asp 150	act Thr	tgg Trp	aac Asn	cgg Arg	ctt Leu 155	ı Asp	t t t Phe	tto Phe	att Ile	gtc Val 160	480
	att Ile	gca Ala	ggg Gly	atg Met	ctg Leu 165	Glu	tat Tyr	tcg Ser	ctg Leu	gac Asp 170	Leu	cag Gln	aac Asn	gtc Val	agc Ser 175	ttc Phe	528
15	tcc Ser	gca Ala	gtc Val	agg Arg 180	Thr	gtc Val	cgt Arg	gtg Vạl	ctg Leu 185	cga Arg	ccg Pro	ctc Leu	agg Arg	gcc Ala 190	att Ile	aac Asn	576
20	cgg Arg	gtg Val	ccc Pro 195	agc Ser	atg Met	cgc Arg	att Ile	ctc Leu 200	gtc Val	aca Thr	tta Leu	ctg Leu	ctg Leu 205	gac Asp	acc Thr	ttg Leu	624
25	CCT Pro	atg Met 210	reu	ggc Gly	aac Asn	gtc Val	ctg Leu 215	ctg Leu	ctc Leu	tgt Cys	ttc Phe	ttc Phe 220	gtc Val	ttt Phe	ttc Phe	atc Ile	672
30	ttt Phe 225	Gly	atc Ile	gtg Val	ggc Gly	gtc Val 230	cag Gln	ctg Leu	tgg Trp	gca Ala	gga Gly 235	ctg Leu	ctt Leu	cgc Arg	aac Asn	cgg Arg 240	720
	tgc Cys	ttc Phe	ctc. Leu	ccc Pro	gag Glu 245	aac Asn	ttc Phe	agc Ser	ctc Leu	ccc Pro 250	ctg Leu	agc Ser	gtg Val	gac Asp	ctg Leu 255	gag Glu	768
35	cct Pro	tat Tyr	tac Tyr	cag Gln 260	aca Thr	gag Glu	aat Asn	gag Glu	gac Asp 265	gag Glu	agc Ser	ccc Pro	ttc Phe	atc Ile 270	tgc Cys	tct Ser	816
40	cag Gln	cct Pro	egg Arg 275	gag Glu	aat Asn	ggc Gly	atg Met	aga Arg 280	tcc Ser	tgc Cys	agg Arg	agt Ser	gtg Val 285	ccc Pro	aca Thr	ċtg Leu	864
45	cgt Arg	999 Gly 290	gaa Glu	ggc Gly	ggt Gly	ggt Gly	ggc Gly 295	cca Pro	ccc Pro	tgc Cys	agt Ser	ctg Leu 300	gac Asp	tat Tyr	gag Glu	acc Thr	912
<i>50</i>	tat Tyr 305	aac Asn	agt Ser	tcc Ser	agc Ser	aac Asn 310	acc Thr	acc Thr	tgt Cys	gtc Val	aac Asn 315	tgg Trp	aac Asn	cag Gln	tac Tyr	tat Tyr 320	960
	acc Thr	aac Asn	tgc Cys	tct Ser	gcg Ala 325	ggc Gly	gag Glu	cac His	aac Asn	ccc Pro 330	ttc Phe	aaa Lys	ggc Gly	gcc Ala	atc Ile 335	aac Asn	1008
55	ttt Phe	gac Asp	aac Asn	att Ile 340	ggc Gly	taț Tyr	gcc Ala	tgg Trp	atc Ile 345	gcc Ala	atc Ile	ttc Phe	cag Gln	gtc Val 350	atc Ile	aca Thr	1056
60	ctg Leu	gag Glu	ggc Gly 355	tgg Trp	gtc Val	gac Asp	atc Ile	atg Met 360	tac Tyr	ttc Phe	gta Val	atg Met	gac Asp 365	gct Ala	cac His	tcc Ser	1104
	ttc Pne	tac Tyr	aac Asn	ttc Phe	atc Ile	tac Tyr	ttc Phe	att Ile	ctt Leu	ctc Leu	atc Ile	atc Ile	gtg Val	ggc Gly	tcc Ser	ttc Phe	1152

		370					375					380					
5.	ttc Phe 385	atg Met	atc Ile	aac Asn	ctg Leu	ege Cys 390	ctg Leu	gtg Val	gtg Val	att Ile	gcc Ala 395	acg Thr	cag Gin	ttc Phe	ccc Ser	gag Glu 400	1200
10	acc Thr	aaa Lys	cag Gln	cgg Arg	gag Glu 405	agt Ser	cag Gln	ctg Leu	atg Met	cgg Arg 410	gag Glu	cag Gln	ogą Arg	gta Val	cga Arg 415	ttc Phe	1248
10	ctg Leu	tcc Ser	aat Asn	gct Ala 420	agc Ser	acc Thr	ctg Leu	gca Ala	agc Ser 425	ttc Phe	tot Ser	gag Glu	cca Pro	ggc Gly 430	agc Ser	tgc Cys	1296
15	tat Tyr	gag Glu	gag Glu 435	cta Leu	ctc Leu	aag Lys	tac Tyr	ctg Leu 440	gtg Val	tac Tyr	atc Ile	ctc Leu	cga Arg 445	aaa Lys	gca Ala	gcc Ala	1344
20															G] À ààà		1392
25															agt Ser		1440 .
30	agc Ser	tgc Cys	act Thr	Arg	tca Ser 485	cac His	cgt Arg	cgt Arg	ctg Leu	tct Ser 490	gtc Val	cac His	cac His	ctg Leu	gtc Val 495	cac His	1488
-,-															acg Thr		1536
35															aat Asn		1584
40															tct Ser	ggg Gly	1632
45	ggc Gly 545	cct Pro	ccg Pro	agg Arg	ggt Gly	gcg Ala 550	gag Glu	tct Ser	gta Val	cac His	agc Ser 555	ttc Phe	tac Tyr	cat His	ġcţ Ala	gac Asp 560	1680
50	tgc Cys	cac His	ttg Leu	gag Glu	cca Pro 565	gtc Val	cgt Arg	tgc Cys	cag Gln	gca Ala 570	ccc Pro	cct Pro	ccc Pro	aga Arg	tgc Cys 575	cca Pro	.1728
															ccc Pro		1776
.55															cta Leu	gtg Val	1824
60															aac Asn		1872
	cca Pro	cct Pro	ggg Gly	ccc Pro	ttc Phe	agc Ser	tcc Ser	atg Met	cac His	aag Lys	ctc Leu	ctg Leu	gaç Glu	aca Thr	cag Gln	agt Ser	. 1920

	625					630					635					640	
5	acg Thr	gga Gly	gcc Ala	tgc Cys	cat His 645	agc Ser	tcc Ser	tgc Cys	aaa Lys	atc Ile 650	tcc Ser	agc Ser	cct Pro	tgc Cys	ser 655	aag Lys	1963
10	gca Ala	gac Asp	agt Ser	gga Gly 660	gcc Ala	tgc Cys	Gly ggg	ccg Pro	gac Asp 665	agt Ser	tgt Cys	ecc Pro	tac Tyr	tgt Cys 670	gcc Ala	egg Arg	2016
	aca Thr	gga Gly	gca Ala 675	gga Gly	gag Glu	cca Pro	gag Glu	tcc Ser 680	gct Ala	gac ·Asp	cat His	gtc Val	atg Met 685	cct Pro	gac Asp	tca Ser	2064
15	gac Asp	agc Ser 690	gag Glu	gct Ala	gtg Val	tat Tyr	gag Glu 695	ttc Phe	aca Thr	cag Gln	gac Asp	gct Ala 700	cag Gln	cac His	agt Ser	gac Asp	2112
20	ctc Leu 705	cgg Arg	gat Asp	ccc Pro	cac His	agc Ser 710	cgg Arg	cgg Arg	cga Arg	cag Gln	cgg Arg 715	agc Ser	ctg Leu	ggc Gly	cca Pro	gat Asp 720	2160
25	gca Ala	gag Glu	cct Pro	agt Ser	tct Ser 725	gtg Val	ctg Leu	gct Ala	ttc Phe	tgg Trp 730	agg Arg	ctg Leu	atc Ile	tgt Cys	gac Asp 735	aca Thr	2208
<i>30</i>	ttc Phe	cgg Arg	aag Lys	atc Ile 740	gta Val	gat Asp	agc Ser	aaa Lys	tac Tyr 745	ttt Phe	ggc Gly	cgg Arg	gga Gly	atc Ile 750	atg Met	atc Ile	2256
	gcc Ala	atc Ile	ctg Leu 755	gtc Val	aat Asn	aca Thr	ctc Leu	agc Ser 760	atg Met	ggc Gly	atc Ile	gag Glu	tac Tyr 765	cac His	gag Glu	cag Glh	2304
35	ccc Pro	gag Glu 770	gag Glu	ctc Leu	acc Thr	aac Asn	gcc Ala 775	ctg Leu	gaa Glu	atc Ile	agc Ser	aac Asn 780	atc Ile	gtc Val	ttc Phe	acc Thr	2352
40	agc Ser 785	ctc Leu	ttc Phe	gcc Ala	ttg Leu	gag Glu 790	atg Met	ctg Leu	ctg Leu	aaa Lys	ctg Leu 795	ctt Leu	gtc Val	tac Tyr	ggt Gly	ccc Pro 800	2400
45	ttt Phe	ggc Gly	tac Tyr	att Ile	aag Lys 805	aat Asn	ccc Pro	tac Tyr	aac Asn	atc Ile 810	ttt Phe	gat Asp	ggt Gly	gtc Val	att Ile 815	gtg Val	2448
50	gtc Val	atc Ile	agt Ser	gtg Val 820	tgg Trp	gag. Glu	att Ile	gtg Val	ggc Gly 825	cag Gln	cag Gln	gga Gly	ggt Gly	ggc Gly 830	ctg Leu	tcg Ser	2496
	gtg Val	ctg Leu	cgg Arg 835	acc Thr	ttc Phe	cgc Arg	ctg Leu	atg Met 840	cgg Arg	gtg Val	ctg Leu	aag Lys	ctg Leu 845	gtg Val	cgc Arg	ttc Phe	2544
<i>55</i>	ctg Leu	ccg Pro 850	gcc Ala	ctg Leu	cag Gln	cgc Arg	cag Gln 855	ctc Leu	gtg Val	gtg Val	ctc Leu	atg Met 860	aag Lys	acc Thr	atg Met	gac Asp	2592
60	aac Asn 865	gtg Val	gcc Ala	acc Thr	ttc Phe	tgc Cys 870	atg Met	ctc Leu	ctc Leu	atg Met	ctg Leu 875	ttc Phe	atc Ile	ttc Phė	atc Ile	ttc Phe ° 880	2640
	agc Ser	atc Ile	ctg Leu	ggc Gly	atg Met	cat His	ctc Leu	ttt Phe	ggt Gly	tgc Cys	aag Lys	ttc Phe	gca Ala	tct Ser	gaa Glu	cgg Arg	2688

				885					89C					895		
5	gat ggg Asp Gl	g gac / Asp	acg Thr 900	ttg Leu	cca Pro	gac Asp	cgg Arg	aag Lys 905	aat Asn	ttc Phe	gac Asp	tcc Ser	ctg Leu 910	ctc Leu	tgg Trp	2736
10	gec ato Ala Ile	gtc Val 915	act Thr	gtc Val	ttt Phe	cag Gln	att Ile 920	ctg Leu	act Thr	cag Gln	gaa Glu	gac Asp 925	egg Trp	aat Asn	aaa Lys	2784
10	gtc ctc Val Let 930	ı Tyr														2832
15	ttc ato Phe Ile 945	gcc Ala	ctc Leu	atg Met	act Thr 950	ttt Phe	ggc Gly	aac Asn	tat Tyr	gtg Val 955	ctc Leu	ttt Phe	aac Asn	Leu	ctg Leu 960	2880
20	gtg gcd Val Ala															2928
25	tct gad Ser Glu															2976
30	gac aga Asp Arc	a aag g Lys 995	aag Lys	cgc Arg	ttg Leu	Ala	ctg Leu 1000	gtg Val	gct Ala	ttg Leu	Gly	gaa Glu 1005	cac His	gcg Ala	gaa Glu	3024
	cta cga Leu Arc 1010	Lys	agc Ser	ctt Leu	Leu	cca Pro 1015	ccc Pro	ctc Leu	atc Ile	Ile	cat His 1020	acg Thr	gct Ala	gcg Ala	aca Thr	3072
35	cca ato Pro Mes 1025	g tca t Ser	cac His	Pro	aag Lys 1030	agc Ser	tcc Ser	agc Ser	Thr	ggt Gly L035	gtg Val	Gly	gaa Glu	Ala	ctg Leu 1040	3120
40	ggc tc: Gly Se:	t ggc r Gly	Ser	cga Arg 1045	cgt Arg	acc Thr	agt Ser	Ser	agt Ser 1 0 50	ggg Gly	tcc Ser	gct Ala	Glu	cct Pro 1055	gga Glý	3168
45	gct gc Ala Al	a His	cat His 1060	gag Glu	atg Met	aaa Lys	Cys	ccg Pro 1065	cca Pro	agt Ser	gcc Ala	Arg	agc Ser 1070	tcc Ser	ccg Pro	3216
50	cac ag His Se	t ccc r Pro 1075	tgg Trp	agt Ser	gcg Ala	Ala	agc Ser 1080	agc Ser	tgg Trp	acc Thr	Seŗ	agg Arg 1085	cgc Arg	tcc Ser	agc Ser	3264
	agg aa Arg As 109	n Ser	ctg Leu	ggc Gly	Arg	gcç Ala 1095	ccc Pro	agc Ser	cta Leu	Lys	cgg Arg 1100	agg Arg	agc Ser	ccg Pro	agc Ser	3312
55	ggg ga Gly Gl 1105	g cgg u Arg	agg Arg	Ser	ctg Leu 1110	ctg Leu	tct Ser	gga Gly	Glu	ggc Gly 1115	cag Gln	gag Glu	agt Ser	Gln	gat Asp 1120	3360
60	gag ga Glu Gl	g gaa u Glu	Ser	tca Ser 1125	gaa Glu	gag Glu	gac Asp	Arg	gcc Ala 1130	agc Ser	cca Pro	gca Ala	Gly	agt Ser 1135	gac Asp	3408
	cat cg His Ar	c cac g His	agg Arg	ggt Gly	tcc Ser	ttg Leu	gaa Glu	agt Arg	gag Glu	gcc Ala	aag Lys	agt Ser	tcc Ser	ttt Phe	gac Asp	3456

			42		C1/03/0/23101
	1140		1145	1150	
5	ctg cot gae act Leu Pro Asp Thr 1155	Leu Gln Val	ccg ggg ctg cac Pro Gly Leu His 1160	cgc aca gcc ago Arg Thr Ala Sec 1165	c ggc 3504 c Gly
10	cgg age tot geo Arg Ser Ser Ala 1170	tot gag cac Ser Glu His 1175	caa gac tgt aat Gln Asp Cys Asn l	ggo aag tog got Gly Lys Ser Ala 1180	tca 3552 a Ser
	ggg cgt ttg gcc Gly Arg Leu Ala 1185	cgc acc ctg Arg Thr Leu 1190	agg act gat gac Arg Thr Asp Asp 1195	ccc caa ctg gat Pro Gln Leu Asp	ggg 3600 Gly 1200
15	Asp Asp Asp Asn	gat gag gga Asp Glu Gly 1205	aat ctg agc aaa Asn Leu Ser Lys 1210	ggg gaa cgc ata Gly Glu Arg Ile 1215	e Gln
20	gcc tgg gtc aga Ala Trp Val Arg 1220	tcc cgg ctt Ser Arg Leu	cct gcc tgt tgc Pro Ala Cys Cys 1225	cga gag cga gat Arg Glu Arg Asp 1230	tcc 3696 Ser
25	tgg tcg gcc tat Trp Ser Ala Tyr 1235	Ile Phe Pro	cct cag tca agg Pro Gln Ser Arg 1240	ttt cgt ctc ctg Phe Arg Leu Leu 1245	tgt 3744 Cys
30	cac cgg atc atc His Arg Ile Ile 1250	acc cac aag Thr His Lys 1255	atg ttt gac cat Met Phe Asp His 1	gtg gtc ctc gtc Val Val Leu Val 260	atc 3792 Ile
ж	atc ttc ctc aac Ile Phe Leu Asn 1265	tgt atc acc Cys Ile Thr 1270	atc gct atg gag Ile Ala Met Glu 1275	Arg Pro Lys Ile	gac 3840 Asp 1280
35	Pro His Ser Ala	gag cgc atc Glu Arg Ile 1285	ttc ctg acc ctc Phe Leu Thr Leu 1290	tcc aac tac atc Ser Asn Tyr Ile 1295	Phe '
40	acg gca gtc ttt Thr Ala Val Phe 1300	cta gct gaa Leu Ala Glu	atg aca gtg aag of Met Thr Val Lys 1305	gtg gtg gca ctg Val Val Ala Leu 1310	ggc 3936 Gly
45	tgg tgc ttt ggg Trp Cys Phe Gly 1315	Glu Gln Ala	tac ctg cgc agc agc agc agc agc agc agc agc ag	agc tgg aat gtg Ser Trp Asn Val 1325	ctg 3984 Leu
50	gac ggc ttg ctg Asp Gly Leu Leu 1330	gtg ctc atc Val Leu Ile 1335	tcc gtc atc gac a Ser Val Ile Asp :	atc ctg gtc tcc Ile Leu Val Ser 340	atg 4032 Met
	gtc tcc gac agc Val Ser Asp Ser 1345	ggc acc aag Gly Thr Lys 1350	atc ctt ggc atg of Ile Leu Gly Met 1 1355	Leu Arg Val Leu	cgg 4080 Arg 1360
<i>55</i>	Leu Leu Arg Thr	ctg cgt cca Leu Arg Pro .365	ctc agg gtc atc a Leu Arg Val Ile S 1370	agc cgg gcc cag Ser Arg Ala Gln 1375	gga 4128 Gly
60	ctg aag ctg gtg Leu Lys Leu Val 1380	gta gag act Val Glu Thr	ctg atg tca tcc of Leu Met Ser Ser I 1385	ctc aaa ccc att Leu Lys Pro Ile 1390	ggc 4176 Gly

aac att gtg gtc att tgc tgt gcc ttc ttc atc att ttt gga att ctc 4224 Asn Ile Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu

	1395	1400	1405	
5	ggg gtg cag ctc t Gly Val Gln Leu F 1410	tto aaa ggg aag Phe Lys Gly Lys 1415	tto tto gtg tgt cag ggt gag gac Phe Phe Val Cys Gin Gly Glu Asp 1420	4272
	acc agg aac atc a Thr Arg Asn Ile 1 1425	act aac aaa tcc Thr Asn Lys Ser 1430	gac tgc gct gag gcc agc tac cga Asp Cys Ala Glu Ala Ser Tyr Arg 1435 1440	4320
10	Tro Val Arg His I	aag tac aac ttt Lys Tyr Asn Phe 145	gac aac ctg ggc cag gct ctg atg Asp Asn Leu Gly Gln Ala Leu Met 1450	4368
15	tcc ctg ttt gtg c Ser Leu Phe Val I 1460	Leu Ala Ser Lys	gat ggt tgg gtt gac atc atg tat Asp Gly Trp Val Asp Ile Met Tyr 1465	4415
20	gat ggg ctg gat o Asp Gly Leu Asp i 1475	gct gtg ggt gtg Ala Val Gly Val 1480	gat cag cag ccc atc atg aac cac Asp Gln Gln Pro Ile Met Asn His 1485	4464
25	aac ccc tgg atg a Asn Pro Trp Met 1	ctg cta tac ttc Leu Leu Tyr Phe 1495	ato too tto oto oto ato gtg goo Ile Ser Phe Leu Leu Ile Val Ala 1500	4512
	ttc ttt gtc ctg . Phe Phe Val Leu . 1505	aac atg ttt gtg Asn Met Phe Val 1510	ggc gtg gtg gag aac ttc cat Gly Val Val Val Glu Asn Phe His 1515 1520	4560
30	Lys Cys Arg Gln	cac cag gag gag His Gln Glu Glu 525	gag gag gcg agg cgg cgt gag gag Glu Glu Ala Arg Arg Arg Glu Glu 1530	4608
35	aag cga cta cgg Lys Arg Leu Arg 1540	agg ctg gag aaa Arg Leu Glu Lys	aag aga agg agt aag gag aag cag Lys Arg Arg Ser Lys Glu Lys Gln 1545 1550	4656
40	atg gcc gaa gcc Met Ala Glu Ala 1555	cag tgc aag ccc Gln Cys Lys Pro 1560	tac tac tct gac tac tcg aga ttc Tyr Tyr Ser Asp Tyr Ser Arg Phe 1565	4704
45	cgg ctc ctt gtc Arg Leu Leu Val 1570	cac cac ctg tgt His His Leu Cys 1575	acc agc cac tac ctg gac ctc ttc Thr Ser His Tyr Leu Asp Leu Phe 1580	4752
-0	atc act ggt gtc Ile Thr Gly Val 1585	atc ggg ctg aad Ile Gly Leu Asn 1590	gtg gtc act atg gcc atg gaa cat Nal Val Thr Met Ala Met Glu His 1595 1600	4800
50	Tyr Gln Gln Pro	cag atc ctg gad Gln Ile Leu Asp 1605	gag gct ctg aag atc tgc aat tac Glu Ala Leu Lys Ile Cys Asn Tyr 1610	4848
55	atc ttt acc gtc Ile Phe Thr Val 1620	atc ttt gtc tt: Ile Phe Val Phe	gag toa gtt tto aaa ott gtg goo e Glu Ser Val Phe Lys Leu Val Ala 1625 1630	4896
60	ttt ggc ttc.cgc Phe Gly Phe Arg 1635	cgt ttc ttc car Arg Phe Phe Gl	g gac agg tgg aac cag ctg gac ctg n Asp Arg Trp Asn Gln Leu Asp Leu 0 1645	4944
	gct att gtg ctt Ala Ile Val Leu	ctg tcc atc at Leu Ser Ile Me	g ggc atc aca ctg gag gag att gag t Gly Ile Thr Leu Glu Glu Ile Glu	4992

	1650	;	•	1655		1660		
5	gtc aat Val Asn 1665	ctg to Leu Se	g stg sed er Leu Pro 1670	o Ile As	c ccc acc n Pro Thr	atc atc cg Tile Tile Ar 1675	t atc atg agg g Ile Met Arg 1680	. 5040
10	gtg ctc Val Leu	egc at Arg Il	t got oga e Ala Arq 1685	gtt ct g Val Le	g aag cto u Lys Leu 1690	Leu Lys Me	g got gtg ggo t Ala Val Gly 1695	5088
	atg cgg Met Arg	gca ct Ala Le 170	u Leu His	acg gte Thr Va	g atg cag 1 Met Gln 1705	god otg od Ala Leu Pr	c cag gtg ggg o Gln Val Gly 1710	5136
15	Asn Leu	gga ct Gly Le 1715	t ctc ttc u Leu Phe	atg tte Met Let 1720	u Leu Phe	ttc atc tt Phe Ile Ph 172	t gca gct ctg e Ala Ala Leu 5	5184
20	ggc gtg Gly Val 1730	gag ct Glu Le	c ttt gga u Phe Gly	gac cto Asp Let 1735	g gag tgt 1 Glu Cys	gat gag ac Asp Glu Th 1740	a cac cct tgt r His Pro Cys	5232
25	gag ggc Glu Gly 1745	ttg gg Leu Gl	t cgg cat y Arg His 1750	Ala Thi	r Phe Arg	aac ttt gg Asn Phe Gl 1755	t atg gcc ttt y Met Ala Phe 1760	5280
<i>30</i>	ctg acc Leu Thr	ctc tt Leu Ph	c cga gtc e Arg Val 1765	tcc act Ser Thr	ggt gac Gly Asp 1770	aac tgg aa Asn Trp Asi	t ggt att atg n Gly Ile Met 1775	5328
	aag gac Lys Asp	acc ct Thr Le 178	u Arg Asp	tgt gad Cys Asp	c cag gag o Gln Glu 1785	too acc tgo Ser Thr Cys	tac aac act Tyr Asn Thr 1790	5376
35	var lie	tcc cc Ser Pr 1795	t atc tac o Ile Tyr	ttt gtg Phe Val 1800	. Ser Phe	gtg ctg acc Val Leu Thi 1805	g gcc cag ttt c Ala Gln Phe	5424
40	gtg ctg Val Leu 1810	gtc aa Val As	n Val Val	ata gct Ile Ala 1815	gtg ctg Val Leu	atg aag cad Met Lys His 1820	c ctg gaa gaa s Leu Glu Glu	5472
45	agc aac Ser Asn 1825	aaa ga Lys Gl	g gcc aag u Ala Lys 1830	gag gag Glu Glu	Ala Glu	ctc gag gcc Leu Glu Ala 1835	gag ctg gag Glu Leu Glu 1840	5520
<i>50</i> -	ctg gag Leu Glu	atg aad Met Ly:	g acg ctc s Thr Leu 1845	agc ccg Ser Pro	cag ccc Gln Pro 1850	cac too coo His Ser Pro	g ctg ggc agc Leu Gly Ser 1855	5568
	ccc ttc Pro Phe	ctc tgc Leu Tri 1860	Pro Gly	gtg gag Val Glu	ggt gtc Gly Val 1865	aac agt act Asn Ser Thr	gac agc cct Asp Ser Pro 1870	5616
55	Lys Pro	ggg gct Gly Ala 875	cca cac a Pro His	acc act Thr Thr 1880	·Ala His	att gga gca Ile Gly Ala 1885	gcc tog ggc Ala Ser Gly	5664
60	ttc tcc Phe Ser 1890	ctt gad Leu Gli	i His Pro	acg atg Thr Met 1895	gta ccc Val Pro	cac ccc gag His Pro Glu 1900	gag gtg cca Glu Val Pro	5712
	gtc ccc Val Pro	cta gga Leu Gly	a cca gas y Pro Asp	ctg ctg Leu Leu	act gtg Thr Val	agg aag tot Arg Lys Ser	ggt gtc agc Gly Val Ser	. 5760

	1905	1910		1915	1923	
5	cgg acg cac Arg Thr His	tot otg coo a Ser Leu Pro A 1925	Asp Ser	tac atg tgc co Tyr Met Cys A: 930	go mat ggg ago - 5 rg Asn Gly Ser 1935	308
10	Thr Ala Glu				co coo aaa goo - 5 au-Pro Lys Ala 1950	956
10					la Asp Thr Ser	904
15	tgc atc cta Cys Ile Leu 1970	Gln Leu Pro I	aaa gat gtg Lys Asp Val 975	cac tat ctg ct His Tyr Leu La 1980	to cag cot cat 5 au Gin Pro His	952
20					ca cot ggo ego 6 co Pro Gly Arg 2000	
25			Pro Leu Arg		ta ata agg act 6 La Ile Arg Thr 2015	5048
30	Asp Ser Leu	gat gtg cag o Asp Val Gln o 2020	ggc ctg ggt Gly Leu Gly 2025	agc cgg gaa ga Ser Arg Glu As	ac ctg ttg tca 6 sp Leu Leu Ser _2030	5096
30					er Ser Phe Trp	5144
35	ggc ggg tcg Gly Gly Ser 2050	Ser Ile Gln V	gtg cag cag Val Gln Gln 055	cgt tcc ggc as Arg Ser Gly I 2060	to cag ago aaa 🦸 le Gln Ser Lys	5192
40	gtc tcc aag Val Ser Lys 2065	cac atc cgc of His Ile Arg 1 2070	ctg cca gcc Leu Pro Ala	cct tgc cca go Pro Cys Pro G 2075	gc ctg gaa ccc 6 ly Leu Glu Pro 2080	5240
45	agc tgg gcc Ser Trp Ala	aag gac cct o Lys Asp Pro 2085	Pro Glu Thr	aga agc agc t Arg Ser Ser L 2090	ta gag ctg gac eu Glu Leu Asp 2095	5288
50	Thr Glu Leu	agc tgg att : Ser Trp Ile : 2100	tca gga gac Ser Gly Asp 2105	ctc ctt ccc a Leu Leu Pro S	gc agc cag gaa er Ser Gln Glu 2110	6336
30	gaa ccc ctg Glu Pro Leu 2115	Phe Pro Arg	gac ctg aag Asp Leu Lys 2120	aag tgc tac a Lys Cys Tyr S 21	er Val Glu Thr	6384
<i>55</i>	cag agc tgc Gln Ser Cys 2130	Arg Arg Arg	cct ggg ttc Pro Gly Phe 135	tgg cta gat g Trp Leu Asp G 2140	aa cag cgg aga lu Gln Arg Arg	6432
60					aa coc cgc cta ln Pro Arg Leu 2160	6480
					gg ggt cct ggg ly Gly Pro Gly	6528

					2169	5				2170	0				217	5	
5	ago Ser	ogg Arg	g cot g Pro	aaq Lys 2180	s rate	a aaa S Lys	a cto	z ago u Ser	c cca r Pro 2183	o Pro	c agt	t ate	c to: e Se:	t ata r Ile 2190	As	c ccc c Pro	6576
10	bio ccd	gaq Glu	; ago 1 Sei 2193	GIF	g ggc Gly	tct Ser	cgc Arc	g ccc g Pro 2200	o Pro	a tgo Cys	agt Ser	cot Pro	gg: Gly 2205	/ Val	t Ego Cys	c ctc s Leu	6624
10	n- 9	agg Arg 2210	Arc	geg Ala	r ccg	gcc Ala	agt Ser 2215	Asp	c tot Ser	aaç Lys	gat Asp	ccc Pro 2220	Ser	g gto val	tco Ser	agc Ser	6672
15	ccc Pro 222	Tre cr	gac Asp	ago Ser	Thr	gct Ala 2230	Ala	tca Ser	ccc Pro	> Ser	cca Pro 2235	Lys	g aaa E Lys	gac Asp	acq Thr	ctg Leu 2240	6720
20	agt Ser	ctc Leu	tct Ser	GLY	ttg Leu 2245	Ser	tct Ser	gac Asp	cca Pro	aca Thr 2250	Asp	atg Met	gac Asp	ccc Pro		·	6762
25	<21 <21	0> 6 1> 6 2> D 3> R	795 NA	s sp												•	
30		1> C		(679	5)												
35	<400 atg Met 1	gac	gag Glu	gag Glu	gag Glu 5	gat Asp	gga Gly	gcg Ala	ggc Gly	gcc Ala 10	gag Glu	gag Glu	tcg Ser	gga Gly	cag Gln 15	ccc Pro	48
40	cgt Arg	agc Ser	ttc Phe	acg Thr 20	cag Gln	ctc Leu	aac Asn	gac Asp	ctg Leu 25	tcc Ser	G] y ggg	gcc Ala	ggg Gly	ggc Gly 30	cgg Arg	cag Gln	96
45	GJ À ààà	ccg Pro	ggg Gly 35	tcg Ser	acg Thr	gaa Glu	aag Lys	gac Asp 40	ccg Pro	ggc Gly	agc Ser	gcg Ala	gac Asp 45	tcc Ser	gag Glu	gcg Ala	144
	gag Glu	ggg Gly 50	ctg Leu	ccg Pro	tac Tyr	ccg Pro	gcg Ala 55	cta Leu	gcc Ala	ccg Pro	gtg Val	gtt Val 60	ttc Phe	ttc Phe	tac Tyr	ttg Leu	192
50	agc Ser 65	cag Gln	gac Asp	agc Ser	cgc Arg	ccg Pro 70	cgg Arg	agc Ser	tgg Trp	tgt Cys	ctc Leu 75	cgc Arg	acg Thr	gtc Val	tgt Cys	aac . Asn 80	240
<i>55</i>	ccg Pro	tgg Trp	ttc Phe	gag Glu	cga Arg 85	gtc Val	agt Ser	atg Met	ctg Leu	gtc Val 90	att Ile	ctt Leu	ctc Leu	aac Asn	tgt Cys 95	gtg Val	288
60	act Thr	ctg Leu	ggt Gly	atg Met 100	ttc Phe	agg Arg	ccg Pro	tgt Cys	gag Glu 105	gac Asp	att Ile	gcc Ala	tgt Cys	gac Asp 110	tcc Ser	cag Gln	336
	cgc Arg	tgc Cys	cgg Arg 115	atc Ile	ctg Leu	cag Gl'n	gcc Ala	ttc Phe 120	gat Asp	gac Asp	ttc Phe	atc Ile	ttt Phe 125	gc: Ala	ttc Phe	ttt .Phe	384

5					gtg Val									432
,		-		-	gga Gly	-				-			-	480
10					ctg Leu 165									528
15					aca Thr									576
20					atg Met									624
25					aac Asn									672
					ggc Gly									720
30					gag Glu 245									768
35					aca Thr									816
40					aat Asn									864
45	_		_		ggt Gly			-	_	_	-			.912
,,	tat Tyr 305				agc Ser									960
50					gcg Ala 325									1008.
55					ggc Gly									1056
60					gtc Val							Ala		1104
			Asn		atc Ile									.1152

5	tto Phe 385	: Met	; acc	aaq Asn	ctg Leu	tgc Cys 390	ren	gtg Val	g gtg . Val	att Ile	gcc Ala 395	Thr	r caq Glr	j tto Phe	tco Ser	gag Glu 400	1200
	acc Thr	aaa Lys	cag Gln	cgg Arg	gag Glu 405	Ser	cag Gln	ctg Leu	atg Met	egg Arg 410	Glu	cag Gln	cg; Arg	gta Val	cga Arg 415	ttc Phe	1248
10	ctg Leu	tcc Ser	aat Asn	gct Ala 420	Ser	acc Thr	ctg Leu	gca Ala	agc Ser 425	Phe	tct Ser	gag Glu	cca Pro	ggc Gly 430	Ser	tgc Cys	1296
15	tat Tyr	gag Glu	gag Glu 435	Leu	ctc Leu	aag Lys	tac Tyr	ctg Leu 440	gtg Val	tac Tyr	atc Ile	ctc Leu	cga Arg 445	Lys	gca Ala	gcc Ala	1344
20	cga Arg	agg Arg 450	ctg Leu	gcc Ala	cag Gln	gtc Val	tct Ser 455	agg Arg	gct Ala	ata Ile	ggc Gly	gtg Val 460	cgg Arg	gct Ala	ggg Gly	ctg Leu	1392 `.
25	ctc Leu 465	Sei	agc Ser	cca Pro	gtg Val	gcc Ala 470	cgt Arg	agt Ser	ggg Gly	cag Gln	gag Glu 475	ccc Pro	cag Gln	ccc	agt Ser	ggc Gly 480	1440
	agc Ser	tgc Cys	act Thr	cgc Arg	tca Ser 485	cac His	cgt Arg	cgt Arg	ctg Leu	tct Ser 490	gtc Val	cac His	cac His	ctg Leu	gtc Val 495	cac His	1488
30	cac His	cat His	cac His	cac His 500	cac His	cat His	cac His	cac His	tac Tyr 505	cac His	ctg Leu	ggt Gly	aat Asn	ggg Gly 510	acg Thr	ctc Leu	1536
35	aga Arg	gtt Val	ccc Pro 515	cgg Arg	gcc Ala	agc Ser	cca Pro	gag Glu 520	atc Ile	cag Gln	gac Asp	agg Arg	gat Asp 525	gcc Ala	aat Asn	G1A āāā	1584
40	tct Ser	cgc Arg 530	cgg Arg	ctc Leu	atg Met	cta Leu	cca Pro 535	cca Pro	ccc Pro	tct Ser	aca Thr	ccc Pro 540	act Thr	ccc Pro	tct Ser	ggg Gly	1632
45	ggc Gly 545	cct Pro	ccg Pro	agg Arg	ggt Gly	gcg Ala 550	gag Glu	tct Ser	gta Val	cac His	agc Ser 555	ttc Phe	tac Tyr	cat His	gct Ala	gac Asp 560	1680
	tgc Cys	cac His	ttg Leu	gag Glu	cca Pro 565	gtc Val	cgt Arg	tgc Cys	cag Gln	gca Ala 570	ccc Pro	cct Pro	ccc Pro	aga Arg	tgc Cys 575	cca Pro	1728
50	tcg Ser	gag Glu	gca Ala	tct Ser 580	ggt Gly	agg Arg	act Thr	gtg Val	ggt Gly 585	agt Ser	ggg	aag Lys	gtg Val	ťac Tyr 590	ccc Pro	act Thr	1776
55	gtg Val	cat His	acc Thr 595	agc Ser	cct Pro	cca Pro	cca Pro	gag Glu 600	ata Ile	ctg Leu	aag Lys	gat Asp	aaa Lys 605	gca Ala	cta Leu	gtg Val	1824
60	gag Glu	gtg Val 610	gcc Ala	ccc Pro	agc Ser	cct Pro	ggg Gly 615	ccc Pro	ccc Pro	acc Thr	ctc Leu	acc Thr 620	agc Ser	ttc Phe	aac Asn	atc Ile	1872
	cca Pro 625	cct Pro	G1y ggg	ccc Pro	ttc Phe	agc Ser 630	tcc Ser	åtg Met	cac His	aag Lys	ctc Leu 635	ctg Leu	gag Glu	aca Thr	cag Gln	agt Ser 6 40	1920

<u>5</u>	acg Thr	gga Gly	gcc Ala	tgc Cys	cat His 645	agc Ser	toc Ser	tgo Cys	aaa Lys	atc Ile 650	tcc Ser	agc Ser	cct Pro	tgo Cys	ser 655	aaç Lys	1968
J	gca Ala	gac Asp	agt Ser	gga Gly 660	gcc Ala	tgc Cys	ggg Gly	eca Pro	gac Asp 665	agt Ser	tgt. Cys	ecc Pro	tac Tyr	ege Cys 670°	gcc Ala	cgg Arg	.2016
10	aca Thr	gga Gly	gca Ala 675	gga Gly	gag Glu	cca Pro	gag Glu	ser 680	gct Ala	gac Asp	cat His	gtc Val	atg Met 685	cct Pro	gac Asp	tca Ser	2064
15									aca Thr								2112
20	ctc Leu 705	cgg Arg	gat Asp	ccc Pro	cac His	agc Ser 710	cgg Arg	cgg Arg	cga Arg	cag Gln	cgg Arg 715	agc Ser	ctg Leu	GJA ādc	cca Pro	gat Asp 720	2160
25	gca Ala	gag Glu	cct Pro	agt Ser	ser 725	gtg Val	ctg Leu	gct Ala	ttc Phe	tgg Trp 730	agg Arg	ctg Leu	atc Ile	tgt Cys	gac Asp 735	aca Thr	2208
23	ttc Phe	cgg Arg	aag Lys	atc Ile 740	gta Val	gat Asp	agc Ser	aaa Lys	tac Tyr 745	ttt Phe	ggc Gly	cgg Arg	gça Gly	atc Ile 750	atg Met	atc Ile	2256
30	gcc Ala	atc Ile	ctg Leu 755	gtc Val	aat Asn	aca Thr	ctc Leu	agc Ser 760	atg Met	ggc Gly	atc Ile	gag Glu	tac Tyr 765	cac His	gag Glu	cag Gln	2304
<i>35</i>	ccc Pro	gag Glu 770	gag Glu	ctc Leu	acc Thr	aac Asn	gcc Ala 775	ctg Leu	gaa Glu	atc Ile	agc Ser	aac Asn 780	atc Ile	gtc Val	ttc Phe	acc Thr	2352
40	agc Ser 785	ctc Leu	ttc Phe	gcc Ala	ttg Leu	gag Glu 790	atg Met	ctg Leu	ctg Leu	aaa Lys	ctg Leu 795	ctt Leu	gtc Val	tac Tyr	ggt Gly	ccc Pro 800	2400
45	ttt Phe	ggc Gly	tac Tyr	att Ile	Lys	Asn	Pro	Tyr	aac Asn	Ile	ttt Phe	gat Asp	ggt Gly	gtc Val	att Ile 815	gtg Val	2448
73	gtc Val	atc Ile	agt Ser	gtg Val 820	tgg Trp	gag Glu	att Ile	gtg Val	ggc Gly 825	cag Gln	cag Gln	gga G <u>ì</u> y	ggt Gly	ggc Gly 830	ctg Leu	tcg Ser	2496
50	gtg Val	ctg Leu	cgg Arg 835	acc Thr	ttc Phe	cgc Arg	ctg Leu	atg Met 840	cgg Arg	gtg Val	ctg Leu	aag Lys	ctg Leu 845	gtg Val	cgc Arg	ttc Phe	2544
55	ctg Leu	ccg Pro 850	gcc Ala	ctg Leu	cag Gln	cgc Arg	cag Gln 855	ctc Leu	gtg Val	gtg Val	ctc Leu	atg Met 860	aag Lys	acc Thr	atg Met	gac Asp	259 2
60	aac Asn 865	gtg Val	gcc Ala	acc Thr	ttc Phe	tgc Cys 870	atg Met	ctc Leu	ctc Leu	atg Met	ctg Leu 875	ttc Phe	atc Ile	ttc Pne	atc Ile	ttc Phe 880	2640
	agc Ser	atc Ile	ctg Leu	ggc Gly	atg Met 885	His	ctc Leu	tt: Phe	ggt Gly	tgc Cys 890	aag Lys	ttc Phe	gca Ala	tct Ser	gaa Glu 895	cgg Arg	2688

ĵ	gat Asp	ggg Gly	gac Asp	acg Thr 900	Leu	cca Pro	gac Asp	cgg Arg	aag Lys 905	Asn	tto Phe	gac Asp	tcc Ser	ctg Leu 910	. Leu	tgg Trp	2736
	gcc Ala	atc Ile	gtc Val 915	Tar	gtc Val	ttt Phe	cag Gln	att Ile 920	Leu	act Thr	cag Gln	gaa Glu	gac Asp 925	Trp	aat Asn	aaa Lys	2784
10	gtc Val	ctc Leu 930	tac Tyr	aac Asn	ggc	atg Met	goc Ala 935	tcc Ser	aca Thr	tcg Ser	tct Ser	tgg Trp 940	Ala	got Ala	sit Leu	tac Tyr	2832
15	ttc Phe 945	atc	gcc Ala	ctc Leu	atg Met	act Thr 950	ttt Pne	ggc Gly	aac Asn	tat Tyr	gtg Val 955	ctic Leu	ttt Phe	aac Asn	ctg Leu	ctg Leu 960	2880
20	gtg Val	gcc Ala	att Ile	ctt Leu	gtg Val 965	gaa Glu	gga Gly	ttc Phe	cag Gln	gca Ala 970	gag Glu	gga Gly	gat Asp	gcc Ala	acc Thr 975	aag Lys	2928
25	tct Ser	gag Glu	tca Ser	gag Glu 980	cct Pro	gat Asp	ttc Phe	ttt Phe	tcg Ser 985	ccc Pro	agt Ser	gtg Val	gat Asp	990 Gly ggt	gat Asp	ggg Gly	2976
	gac Asp	aga Arg	aag Lys 995	aag Lys	cgc Arg	ttg Leu	Ala	ctg Leu 1000	gtg Val	gct Ala	ttg Leu	Gly	gaa Glu 1005	cac His	gcg Ala	gaa Glu	3024
30	ьeu	cga Arg 010	aag Lys	agc Ser	ctt Leu	Leu	cca Pro 1015	ccc Pro	ctc Leu	atc Ile	Ile	cat His LO20	acg Thr	gct Ala	gcg Ala	aca Thr	3072
35	cca Pro 1025	Mer	tca Ser	cac His	Pro	aag Lys 1030	agc Ser	tcc Ser	agc Ser	Thr	ggt Gly L035	gtg Val	ggg Gly	gaa Glu	Ala	ctg Leu 1040	3120
40	ggc Gly	tct Ser	ggc Gly	Ser	cga Arg 045	cgt Arg	acc Thr	agt Ser		agt Ser .050	ggg Gly	tcc Ser	gct Ala	Glu	cct Pro 1055	gga Gly	3168
45	gct Ala	gcc' Ala	HIS	cat His .060	gag Glu	atg Met	aaa Lys	Cys	ccg Pro .065	cca Pro	agt Ser	gcc Ala	Arg	agc Ser .070	tcc Ser	ccg Pro	3216
2.	Cac	Ser	ccc Pro 075	tgg Trp	agt Ser	gcg Ala	Ala	agc Ser .080	agc Ser	tgg Trp	acc Thr	Ser	agg Arg .085	ege Arg	tcc Ser	agc Ser	3264
50	agg Arg 1	aac Asn 090	agc [.] Ser	ctg Leu	ggc Gly	Arg	gcc Ala 095	ccc Pro	agc Ser	cta Leu	Lys	cgg Arg 100	agg Arg	agc Ser	ccg Pro	agc Ser	3312
<i>55</i>	ggg Gly 1105	gag Glu	cgg Arg	agg Arg	Ser	ctg Leu 110	ctg Leu	tct Ser	gga Gly	Glu	ggc Gly 115	cag Gln	gag Glu	agt Ser	Gln	gat Asp 120	3360
60	gag Glu	gag Glu	gaa Glu	Ser	tca Ser 125	gaa Glu	gag Glu	gac Asp	Arg	gcc Ala 130	agc Ser	cca Pro	gca Ala	Gly	agt Ser 135	gac Asp	3408
	cat d His	ege Arg	Hıs	agg Arg 140	ggt Gly	tcc Ser	ttg Leu	Glu	cgt Arg 145	gag Glu	gcc Ala	aag Lys	Ser	tcc Ser 150	ttt Phe	gac Asp	3456

5	ctg cct Leu Pro 1	gac ac Asp Th 155	t ctg r Leu	cag (Gln \	/al P	ecg Pro 160	ggg Gly	ctg Leu	cac His	Arg	aca Thr 165	gos Ala	agc Ser	ggc Gl _, y	3504
J	cgg agc Arg Ser 1170	tct gc Ser Al	c tot a Ser	Glu :	cac c His G 175	saa Bin	gac Asp	tgt Cys	Asn	ддс Gly .180	aag Lys	tcg Ser	gct Ala	tca Ser	3552
10	ggg cgt Gly Arg 1185	ttg gc Leu Al	a Arg	acc of Thr 1	ctg a Leu A	yrg agg	act Thr	Asp	gac Asp 195	ccc Pro	caa Gln	ctg Leu	Asp	200 Gly ggg	3600
15	gat gat Asp Asp	gac aa Asp As	t gat n Asp 1205	gag (Glu (gga a Gly A	aat Asn	Leu	agc Ser 210	aaa Lys	Gly	gaa Glu	Arg	ata Ile 215	caa Gln	3648
20	gcc tgg Ala Trp	gtc ag Val Ar 122	g Ser	cgg (Arg)	ctt c Leu f	Pro	gcc Ala 225	tgt Cys	tgc Cys	cga Arg	Glu	cga Arg 230	gat Asp	tcc Ser	3696
25	tgg tcg Trp Ser	gcc ta Ala Ty 1235	t atc r Ile	ttt (Phe	Pro E	ect Pro 240	cag Gln	tca Ser	agg Arg	Phe	cgt Arg 245	ctc Leu	ctg Leu	tgt Cys	3744
23	cac cgg His Arg 1250	atc at Ile Il	c acc e Thr	His :	aag a Lys N 255	atg Met	ttt Phe	gac Asp	His	gtg Val 260	gtc Val	ctc Leu	gtc Val	atc Ile	3792
30	atc ttc Ile Phe 1265	ctc aa Leu As	n Cys	atc Ile 270	acc a Thr 1	atc Ile	gct Ala	Met	gag Glu 275	cgc Arg	ccc Pro	aaa Lys	Ile	gac Asp .280	3840
35	ccc cac Pro His	agc gc Ser Al	t gag a Glu 1285	cgc Arg	atc t Ile i	ttc Phe	Leu	acc Thr 290	ctc Leu	tcc Ser	aac Asn	Tyr	atc Ile 1295	ttc Phe	3888
40	acg gca Thr Ala	gțc tt Val Ph 130	e Leu	gct Ala	gaa a Glu b	Met	aca Thr 305	gtg Val	aag Lys	gtg Val	Val	gca Ala 1310	ctg Leu	ggc Gly	3936
45	tgg tgc Trp Cys	ttt go Phe Gl 1315 ·	gg gag .y Glu	cag Gln	Ala 1	tac Tyr 320	ctg Leu	cgc Arg	agc Ser	Ser	tgg Trp 1325	aat Asn	gtg Val	ctg Leu	3984
13	gac ggc Asp Gly 1330	Leu Le	g gtg eu Val	Leu	atc Ile 335	tcc Ser	gtc Val	atc Ile	Asp	atc Ile 1340	ctg Leu	gtc Vại	tcc Ser	atg Met	4032
50	gtc tcc Val Ser 1345	gac ac .Asp Se	er Gly	acc Thr 1350	aag Lys	atc Ile	ctt Leu	Gly	atg Met 1355	ctg Leu	agg Arg	gtg Val	Leu	cgg Arg 1360	4080
55	ctg ctg Leu Leu	cgg ac Arg Ti	cc ctg nr Leu 1365	cgt Arg	cca Pro	ctc Leu	Arg	gtc Val 1370	atc Ile	agc Ser	cgg Arg	Ala	cag Gln 1375	gga Gly	4128
60	ctg aag Leu Lys	ctg g Leu V	al Val	gag Glu	act Thr	Leu	atg Met 1385	tca Ser	tcc Ser	ctc Leu	Lys	ccc Pro 1390	Ile	Gly	4176
	aac att Asn Ile	gtg g Val V 1395	tc att al Ile	tgc Cys	Cys	400 Ala gcc	ttc Phe	ttc Phe	atc Ile	Ile	ttt Phe 1405	Gly	att Ile	ctc Leu	4224

5	ggg gtg cag ctc ttc aaa ggg aag ttc ttc gtg tgt cag ggt gag gac Gly Val Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp 1410 1415 1420.	4272
	acc agg aac atc act aac aaa too gac tgo got gag goo ago tao oga Thr Arg Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg 1425 1430 1435 1440	4320
10	tgg gtc cgg cac aag tac aac ttt gac aac ctg ggc cag gct ctg atg Trp Val Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met 1445 1450 1455	4368
15	too otg ttt gtg otg god too aag gat ggt tgg gtt gad atd atg tat Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr 1460 1465 1470	4416
20	gat ggg ctg gat gct gtg ggt gtg gat cag cag ccc ate atg aac cac Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His 1475 1480 1485	4464
<i>25</i>	aac ccc tgg atg ctg cta tac ttc atc tcc ttc ctc ctc atc gtg gcc Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala 1490 1495 1500	4512
	tto ttt gto otg aac atg ttt gtg ggc gtg gtg gtg gag aac tto cat Phe Phe Val Leu Asn Met Phe Val Gly Val Val Glu Asn Phe His 1505 1510 1515	4560
30	aag tgc aga cag cac cag gag gag gag gcg agg cgg c	4608
35	aag cga cta cgg agg ctg gag aaa aag aga agg aat cta atg ttg gac Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Asn Leu Met Leu Asp 1540 1545 1550	4656
40	gat gta att gct tcc ggc agc tca gcc agc gct gcg tca gaa gcc cag Asp Val Ile Ala Ser Gly Ser Ser Ala Ser Ala Ala Ser Glu Ala Gln 1565	4704
45	tgc aag ccc tac tac tct gac tac tcg aga ttc cgg ctc ctt gtc cac Cys Lys Pro Tyr Tyr Ser Asp Tyr Ser Arg Phe Arg Leu Leu Val His 1570 1580	4752
	His Len Cve The Son Hie Tun Inc. And I am Div. Ti and Till Inc.	4800
50	ggg ctg aac gtg gtc act atg gcc atg gaa cat tac cag cag ccc cag Gly Leu Asn Val Val Thr Met Ala Met Glu His Tyr Gln Gln Pro Gln 1605 1610 1615	4848
55	atc ctg gac gag gct ctg aag atc tgc aat tac atc ttt acc gtc atc Ile Leu Asp Glu Ala Leu Lys Ile Cys Asn Tyr Ile Phe Thr Val Ile 1620 1630	4896
60	ttt gtc ttt gag tca gtt ttc aaa ctt gtg gcc ttt ggc ttc cgc cgt Phe Val Phe Glu Ser Val Phe Lys Leu Val Ala Phe Gly Phe Arg Arg 1635 1640 1645	4944
	ttc ttc cag gac agg tgg aac cag ctg gac ctg gct att gtg ctt ctg Phe Phe Gln Asp Arg Trp Asn Gln Leu Asp Leu Ala Ile Val Leu Leu 1650 1655 1660	4992

5	tcc atc Ser Ile 1665	atg ggc Met Gly	atc aca Ile Thr 1670	cig gag Leu Glu	Glu Ile	gag gtc Glu Val 1675	aat otg Asn Leu	tog ctg Ser Leu 1680	.5040
•	ccc atc Pro Ile	Asn Pro	acc atc Thr Ile 1685	atc cgt Ile Arg	atc atg Ile Met 1690	agg gtg Arg Val	Leu Arg	att gct Ile Ala .695	5033
10	cga gtt Arg Val	ctg aag Leu Lys 1700	ctg ttg Leu Leu	Lys Met	gct gtg Ala Val 1705	ggc atg Gly Met	cgg gca Arg Ala 1710	ctg ctg Leu Leu	5136
15	His Thr	gtg atg Val Met 715	cag gcc Gln Ala	ctg ccc Leu Pro 1720	Gln Val	ggg aac Gly Asn	ctg gga Leu Gly .725	ctt ctc Leu Leu	5134
20	ttc atg Phe Met 1730	tta ttg Leu Leu	Phe Phe	atc ttt Ile Phe 1735	gca gct Ala Ala	ctg ggc Leu Gly 1740	gtg gag Val Glu	ctc ttt Leu Phe	5232
25	gga gac Gly Asp 1745	ctg gag Leu Glu	tgt gat Cys Asp 1750	gag aca Glu Thr	His Pro	tgt ⁻ gag Cys Glu 1755	ggc ttg Gly Leu	ggt cgç Gly Arg 1760	5280
23	cat gcc His Ala	Thr Phe	agg aac Arg Asn 1765	ttt ggt Phe Gly	atg gcc Met Ala 1770	ttt ctg Phe Leu	Thr Leu	ttc cga Phe Arg 1775	5328
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	gat ggg ctg gat gct gtg ggt gtg gat cag cag ccc atc atg aac cac Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His 1475 1480 1485	4464
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35	aag tgc aga cag cac cag gag gag gag gag gcg agg cgt gag gag Lys Cys Arg Gln His Gln Glu Glu Glu Ala Arg Arg Arg Glu Glu 1525 1530 1535	4608
40	aag cga cta cgg agg ctg gag aaa aag aga agg agt aag gag aag cag Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Ser Lys Glu Lys Gln 1540 1545 1550	4656
40	atg gcc gat cta atg ttg gac gat gta att gct tcc ggc agc tca gcc Met Ala Asp Leu Met Leu Asp Asp Val Ile Ala Ser Gly Ser Ser Ala 1555 1560 1565	4704
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	gaa cat tac cag cag ccc cag atc ctg gac gag gct ctg aag atc tgc Glu His Tyr Gln Gln Pro Gln Ile Leu Asp Glu Ala Leu Lys Ile Cys 1620 1625 1630	4896
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<u>ي</u>	Asp Leu Ala Ile Val Leu Leu Ser Ile Met Gly Ile Thr Leu Glu Glu 1665 1670 1680	5040
10	1685 1690 The Ile Ile Arg Ile	5088
15	atg agg gtg ctc cgc att gct cga gtt ctg aag ctg ttg aag atg gct Met Arg Val Leu Arg Ile Ala Arg Val Leu Lys Leu Leu Lys Met Ala 1700 1705	5136
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35	1780 1785 1790	5376
40	1795 Led Arg Asp Cys Asp Gln Glu Ser Thr Cys Tyr	5424
45	1810 1815 The Val Ser Phe Val Leu Thr Ala	5472
43	1825 1830 1835 Leu Met Lys His Leu 1840	5520
50	1845 1850 1855	5568
55	1860 1865 1870	616
60	1875 1830 1885	664
	age cet aag eet ggg get eea eae aet gee eae att gga gea gee 5 Ser Pro Lys Pro Gly Ala Pro His Thr Thr Ala His Ile Gly Ala Ala 1890 1895 1900	712

	tog ggo Ser Gly 1905	tto Phe	tos (Ser i	ctt g Leu G 19	lu His	003 Pro	acg Thr	Met	gta Vai 915	ccc Pro	Cac His	con Pro	Glu	gag Glu 1920	5760
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10	gtc agc Val Ser	Arg	acg o Thr i 940	cac to His S	ct ctg er Leu	Pro	aat Asn 1945	gac Asp	agc Ser	tac Tyr	Met	tgc Cys .950	yrd cic	aat Asn	5856
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40	ttc tgg Phe Trp 2065	Ğİv	Glv	Ser S	er Ile	Gla	Val	Gln	Gln	Arg	Ser	Gly	Ile	cag Gln 2080	6240
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55	ctg gac Leu Asp	acg Thr 2115	gag Glu	ctg a Leu S	er Trp	att Ile 2120	tca Ser	gga Gly	gac Asp	Leu	ctt Leu 2125	ccc Pro	agc Ser	agc Ser	6384
. 60	cag gaa Gln Glu 2130	Ğlu	ccc Pro	ctg t Leu P	tc cca he Pro 2135	Arg	gac Asp	ctg Leu	Lys	aag Lys 2140	tgc Cys	tac Tyr	agt Ser	gta Val	6432
UI		63.6	200	a	.gg cgc	acc	cct	aaa	ttc	Eas	cta	gat	gaa	caq	6480

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25	acg ctg agt ctc tct ggt ttg tct tct gac cca aca gac atg gac ccc 681 Thr Leu Ser Leu Ser Gly Leu Ser Ser Asp Pro Thr Asp Met Asp Pro 2260 2265 2270	. 6
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45	cgt agc ttc acg cag ctc aac gac ctg tcc ggg gcc ggg ggc cgg cag 96 Arg Ser Phe Thr Gln Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Gln 20 25 30	
50	ggg ccg ggg tcg acg gaa aag gac ccg ggc agc gcg gac tcc gag gcg 144 Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala 35 40 45	
55	gag ggg ctg ccg tac ccg gcg cta gcc ccg gtg gtt ttc ttc tac ttg 192 Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu 50 55 60	
	age cag gac age ege egg age tgg tgt etc ege aeg gte tgt aac 240 Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn 65 70 75 80	
60	ccg tgg ttc gag cga gtc agt atg ctg gtc att ctt ctc aac tgt gtg 288 Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val 85 90 95	
	act ctg ggt atg ttc agg ccg tgt gag gac att gcc tgt gac tcc cag 336	

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	aaa Lys 145	tgt Cys	tac Tyr	ctg Leu	gga Gly	gac Asp 150	act Thr	tgg Trp	aac Asn	cgg Arg	ctt Leu 155	gac Asp	ttt Phe	ttc Phe	att Ile	gtc Val 160	430
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	ct	g ga	g gg	c tg	g gt	c ga	c at	c at	g ta	c tt	c gt	a at	g ga	c gc	t ca	c tcc	1104

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			- 110	42	_		r re	u AI	42	25	ne	Ser	G1:	ı Pr	o G1 43	y S∈ 0	er	Cys	1296
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رد	gcc Ala	atc Ile	ctg Leu 755	gtc Val	aat Asn	aca Thr	ctc Leu	agc Ser 760	atg Met	ggc Gly	atc Ile	gag Glu	tac Tyr 765	cac His	gag Glu	cag Gln	2304
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15												gaa Glu				aaa Lys	2784
13												tgg Trp 940					2832
20												ctc Leu					2880
25												gga Gly					2928
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	gag	gag	gaa	agt	tca	gaa	gag	gas	cgg	gcc	agc	cca	gca	ggc	agt	gac	3408

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10	ctg cct gac Leu Pro Asp 1155	Thr Leu Gln Val	ccg ggg ctg ca Pro Gly Leu Hi 1160	ac ego aca goo ago Is Arg Thr Ala Ser 1165	ggc 3504 Gly
1.5	cgg agc tct Arg Ser Ser 1170	gcc tct gag cac Ala Ser Glu His 1175	caa gac tgt aa Gln Asp Cys As	at ggc aag tog got sn Gly Lys Ser Ala 1180	tca 3552 Ser
15	ggg cgt ttg Gly Arg Leu 1185	gcc cgc acc ctg Ala Arg Thr Leu 1190	agg act gat ga Arg Thr Asp As 119	ac ccc caa ctg gat sp Pro Gin Leu Asg 95	ggg 3600 Gly 1200
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25	Ala Trp Val	aga tcc cgg ctt Arg Ser Arg Leu 1220	cct gcc tgt to Pro Ala Cys Cy 1225	gc cga gag cga gat ys Arg Glu Arg Asp 1230	tcc 3696 Ser
30	tgg tcg gcc Trp Ser Ala 1235	Tyr Ile Phe Pro	cct cag tca ac Pro Gln Ser Ar 1240	gg ttt ogt oto oto og Phe Arg Leu Lev 1245	g tgt 3744 ı Cys
25	cac cgg atc His Arg Ile 1250	atc acc cac aag Ile Thr His Lys 1255	atg ttt gac ca Met Phe Asp Hi	at gtg gtc ctc gtc is Val Val Leu Val 1260	atc 3792 Lile
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40	ccc cac agc Pro His Ser	gct gag cgc atc Ala Glu Arg Ile 1285	ttc ctg acc ct Phe Leu Thr Le 1290	to too aac tac ato eu Ser Asn Tyr Ilo 129	e Pne
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. 55	gtc tcc gac Val Ser Asp 1345	agc ggc acc aag Ser Gly Thr Lys 1350	atc ctt ggc a Ile Leu Gly M 13	tg ctg agg gtg ct et Leu Arg Val Le 55	g cgg 4080 u Arg 1360
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	ctg aag ctg	gtg gta gag act	ctg atg tca t	cc ctc aaa ccc at	t ggc 4176

	Leu Lys Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly 1380 1385 1390
	and att gtg gtd att tgd tgt gdd ttd ttd atd att ttt gga att ctd 3 Ash Ile Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu 1395 1400 1405
I	ggg gtg cag ctc ttc aaa ggg aag ttc ttc gtg tgt cag ggt gag gac 4272 Gly Val Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp 1410 1420
12	
2.0	tgg gtc cgg cac aag tac aac ttt gac aac ctg ggc cag gct ctg atg 4368 Trp Val Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met 1445 1450 1455
20	Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr 1460 1465 1470
25	1475 1480 Asp Gln Gln Pro Ile Met Asn His
30	aac ccc tgg atg ctg cta tac ttc atc tcc ttc ctc atc gtg gcc 4512 Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala 1490 1495 1500
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40	aag tgc aga cag cac cag gag gag gag gcg agg cgg c
40	aag cga cta cgg agg ctg gag aaa aag aga agg aaa gcc cag tgc aag 4656 Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Lys Ala Gln Cys Lys 1540 1545 1550
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	gac gag gct ctg aag atc tgc aat tac atc ttt acc gtc atc ttt gtc 4848 Asp Glu Ala Leu Lys Ile Cys Asn Tyr Ile Phe Thr Val Ile Phe Val 1605 1610 1615
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	cag gac agg tgg aac cag ctg gac ctg gct att gtg ctt ctg tcc atc 4944

	Gln As	p Arg 1635	Trp	Asn	Gln		Asp 1640	Leu	Ala	Ile		Leu 645	Leu	Ser	Ile	
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25	ctg ga Leu Gl 173	u Cys	gat Asp	gag Glu	Thr	cac His L735	cct Pro	tgt Cys	gag Glu	Gly	ttg Leu 1740	ggt Gly	cgg Arg	cat His	gcc Ala	5232
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	gag gg Glu Gl	y Val	aac Asn 1860	agt Ser	act Thr	gac Asp	Ser	cct Pro 1865	aag Lys	cct Pro	ggg Gly	Ala	cca Pro 1870	cac His	acc Thr	5616
60	act go Thr Al	c cac a His 1875	Ile	gga Gly	gca Ala	Ala	teg Ser 1880	ggc Gly	ttc Phe	tcc Ser	Leu	gag Glu 1885	cac His	ccc Pro	acg Thr	5664
	atg gt	a ccc	cac	ccc	gag	gaç	gtş	сса	gtc	ccc	cta	gga	сса	gac	ctg	5712

	Met Val Pro His Pro Glu Glu Val Pro Val Pro Leu Gly Pro Asp Leu 1390 1895 1900	
	Ctg act gtg agg aag tot ggt gtc agc cgg acg cac tot ctg ccc aat Leu Thr Val Arg Lys Ser Gly Val Ser Arg Thr His Ser Leu Pro Asn 1905 1910 1915	5760
10	1930 1935	5808
15		5856
•	gtt cac too caa oca goa gac aco ago tgo ato ota cag ott coo aaa Val His Ser Gln Pro Ala Asp Thr Ser Cys Ile Leu Gln Leu Pro Lys 1955 1960 1965	5904
20	Asp Val His Tyr Leu Leu Gln Pro His Gly Ala Pro Thr Trp Gly Ala 1970 1975 1980	5952
25	atc cct aaa cta ccc cca cct ggc cgc tcc cct ctg gct cag agg cct Ile Pro Lys Leu Pro Pro Pro Gly Arg Ser Pro Leu Ala Gln Arg Pro 1985 1990 1995 2000	6000
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	cct ctg acc cgg tcc tca tcc ttc tgg ggc ggg tcg agc atc cag gtg Pro Leu Thr Arg Ser Ser Ser Phe Trp Gly Gly Ser Ser Ile Gln Val 2035 2040 2045	6144
40	cag cag cgt too ggo ato cag ago aaa gto too aag cao ato cgo otg Gln Gln Arg Ser Gly Ile Gln Ser Lys Val Ser Lys His Ile Arg Leu 2050 2055 2060	6192
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	ctg aag aag tgc tac agt gta gag acc cag agc tgc agg cgc agg cct . 6 Leu Lys Lys Cys Tyr Ser Val Glu Thr Gln Ser Cys Arg Arg Pro 2115 2120 2125	5384
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	Leu As 2145	sp Se.	Gly		Gin 2150	220	Arg	Leu		Pro 2155	Ser	Pro	Ser		Leu 2160	
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15	ccc cc Pro Pr	ca tg ro Cy: 219	s Ser	cct Pro	ggt Gly	Val	tgs Cys 2200	ctc Leu	agg Arg	agg Arg	Arg	gcg Ala 2205	ccg Pro	gcc Ala	agt Ser	6624
15	gac to Asp Se 221	er Ly:	g gat s Asp	ccc Pro	Ser	gtc Val 2215	tcc Ser	agc Ser	ccc Pro	Leu	gac Asp 2220	agc Ser	acg Thr	gct Ala	gcc Ala	6672
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	<213>	Homo	sapi	ens											-	•
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	<220><221><221><222><400>atg acmet Ti	CDS (1). 9 cc gaahr Gl	g ggc u Gly	gca Ala 5	Arg	Ala	Ala	Asp	Glu 10	Val ggc	Arg	Val	Pro	Leu 15 gag	Gly	48 96
40 45	<220> <221> <222> <400> atg acmed Till 1	CDS (1). 9 cc ga hr Gl gc cc rg Pr	g ggc g Gly tgg Trp 20 ggg a Gly	gca Ala 5 ccc Pro	Arg tgc Cys	Ala ggc Gly	Ala gtt Val gga	Asp ggt Gly 25	Glu 10 ggg Gly	Val ggc Gly ttc	gtc Val	val ccc Pro	gga Gly 30	Leu 15 gag Glu gtg	Gly ccc Pro	
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. 5			11	.5		- y - 1.1\	- C .	1.	20	PIC	cy:	5 61	u As	sp V 1	'al 25	Glu	Су	c ggo	,
10		13	0	9 0]	, 0 . 1.2	, 11	13	35	ru	АІА	₽n∈	AS	р АЈ 14	la P 10	he	Ile	Ρ'n	c gcc e Ala	
1.=	145				0_	15	0			гàг	мес	. va. 15:	1 A1	a L	eu (Gly	Le	g ttc u Phe 160	480
15	•				16	5	u Gi	у ма	·Ω	IUL	170	Ası	ı Ar	g L	∋u A	Asp	Phe 175		528
20				18	0	,	c nc	c GI]	185	ser	Let	As	p Gl	y H 1	90	Asr	gtg Val	576
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9.5	225				. 500	230	nsi N	ı val	بد ا	eu	Leu	235	Cys	Ph	e Pl	ne	Val	Phe 240	720
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40	aac Asn i	,	-,-	260	bea	nsp	Set	AIG	26	65	/al .	Arg	Asn	Ası	n As 27	n 1	Leu	Thr	816
45	ttc (Phe 1		27Š		- , -	- , -	01	280	G	Lu c	oru (этУ	GIU	285	AS	n E	Pro	Phe	864
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	Pro G 305	gc ' Sly .	cgc Arg	cgc Arg	gac Asp	gtg Val 310	cgc Arg	atg Met	cc Pr	c t	ys 1	acc Chr 315	ctg Leu	ggc Gly	tg Tr	g g p G	lu.	gcc Ala 320	960
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60	atc a Ile A	ac t sn 1		aac Asn 340	cag Gln	tac Tyr	tac Tyr	aac Asn	gt. Va. 34:	T C.	gc c ys A	gc :	tcg Ser	gçt Gly	gad Asp 350	S S	cc a er 1	aac Asn	1056
	Pro H.	ac a is A	aac (Asn (ggt Gly	gcc Ala	atc Ile	aac Asn	ttc Phe	ga Ası	c aa p As	ac a sn T	cc t hr (gc Cys	tac Tyr	gco Ala	to T	gg a	itt []e	1104

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	cac His	cat His	gaa Glu	cta Leu	ccc Pro	cac His	gat Asp	cct Pro	gcc Ala	ctc Leu	agg Arg	ggt Gly	ggg Gly	cag Gln	cgg Arg	caa Gln	1872

		6	10				6	15					62	0					
5	62	25		. 5		cc cg co Ar 63	9 1,	12 6.	ii G	TÀ (31 U	va. 635	L GI	y Ar	g Tr	pT.	hr	Ala 640	1920
10		,		ig G.	64		Ϋ́ FΙ	O Lie	8U 5	ez 1	550	Asr	. Se.	r Pr	o As	p P:	ro 55	Тут	1968
	ga Gl	g aa u Ly	ng at /s II	e Pr	Onl	t gt s Va	g go l Al	c go a Gl	g ga Ly G1 66	Lu H	is	gga Gly	CEO Le	g gg	c ca y Gl 67	n Al	cc La	cct Pro	2016
15	- ,	,	67	5	1 01	c ct y Le	u 5e	68 68	0	:0 C	ys	Pro	Let	Pro 695	Se	r Pr	0	Pro	2064
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<i>30</i>				y AL	725		ığı	ובט	u Pn	e Tr 73	ir (äln	Asp	Val	Arc	73!	s G 5	Зlу	2208
	gac Asp	cgo Aro	tg g Tr	g gad P Asp 740) FIC	acg Thr	cga Arg	cca Pro	9 CC0 Pro 745	o Ar	jt g ig Æ	gcg Ala	acg Thr	gac Asp	aca Thr 750	Pro	ag oG	gc	2 2 56
35	cca Pro	G17 aad	/ Pro 755	, 617	ago Ser	ccc Pro	cag Gln	cgc Arg 760	arq	g gc g Al	a c	ag Sln	cag Gln	agg Arg 765	gca Ala	gco Ala	C C	cg ro	2304
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50	gcc Ala	atc Ile	ctt Leu	gtc Val	aac Asn 805	acg Thr	ctg Leu	agc Ser	atg Met	gg Gl 81	y V	tg (gag Glu	tac Tyr	cat His	gag Glu 815	ca Gl	ig In	2448
	ccc Pro	gag Glu	gag Glu	ctg Leu 820	act Thr	aat Asn	gct Ala	ctg Leu	gag Glu 825	ato Ile	c ac	gc a er A	aac Asn	atc Ile	gtg Val 830	ttc Phe	ac Th	ic ir	2496
<i>55</i>	agc Ser	atg Met	ttt Phe 835	gcc Ala	ctg Leu	gag Glu	atg Met	S40 Ctg	ctg Leu	aaç Lys	j ct	ig c	eu .	gcc Ala 845	tgc Cys	ggg Gly	cc Pr	t	2544
60		ggc Gly 850	tac Tyr	atc Ile	cgg Arg	aac Asn	ccg Pro 855	tac Tyr	aac Asn	ato	t t	ie A	sp (ggc Gly	atc Ile	atc Ile	gt Va	G 1	2592
	gtc Val	atc Ile	agc Ser	gtc Val	tgg Trp	gag Glu	atc Ile	gtg Val	ggg Gly	cag Gln	gc Al	g g .a.A	ac o	ggt (Gly (ggc Gly	ttg Leu	tc Se	t r	2640

	865					870					875					890	
5	gtg Val	ctg Leu	ogo Arg	acc Thr	ttc Phe 885	cgg Arg	ctg Leu	ctg Leu	cgt Arg	gtg Val 890	ctg Leu	aag Lys.	ctg Leu	gig Val	ege Arg 895	ttt Phe	2638
10	ctg Leu	cca Pro	gcc Ala	ctg Leu 900	cgg Arg	cgc Arg	cag Gln	ctc Leu	gtg Val 905	gtg Val	ctg Leu	gtg Val	aag Lys	acc Thr 910	atg Met	gac Asp	2736
10	aac Asn	gtg Val	gct Ala 915	acc Thr	ttc Phe	tgc Cys	acg Thr	ctg Leu 920	ctc Leu	atg Met	ctc Leu	ttc Phe	att Ile 925	ttc Phe	atc Ile	ttc Phe	2784
15	açc Ser	atc Ile 930	ctg Leu	ggc Gly	atg Met	cac His	ctt Leu 935	ttc Phe	G] y	tgc Cys	aag Lys	ttc Phe 940	agc Ser	ctg Leu	aag Lys	aca Thr	2832
20	gac Asp 945	acc Thr	gga Gly	gac Asp	acc Thr	gtg Val 950	cct Pro	gac Asp	agg Arg	aag Lys	aac Asn 955	ttc Phe	gac Asp	tcc Ser	ctg Leu	ctg Leu 960	2880
<i>25</i> .	tgg Trp	gcc Ala	atc Ile	gtc Val	acc Thr 965	gtg Val	ttc Phe	cag Gln	atc Ile	ctg Leu 970	acc Thr	cag Gln	gag Glu	gac Asp	tgg Trp 975	aac Asn	2928
<i>30</i>	gtg Val	gtc Val	ctg Leu	tac Tyr 980	aac Asn	ggc Gly	atg Met	gcc Ala	Ser 985	acc Thr	tcc Ser	tcc Ser	tgg Trp	gcc Ala 990	gcc Ala	ctc Leu	2976
30	tac Tyr	ttc Phe	gtg Val 995	gcc Ala	ctc Leu	atg Met	Thr	ttc Phe 1000	ggc Gly	aac Asn	tat Tyr	Val	ctc Leu 1005	ttc Phe	aac Asn	ctg Leu	3024
<i>35</i>	Leu	gtg Val 1010	gcc Ala	atc Ile	ctc Leu	Val	gag Glu 1015	ggc Gly	ttc Phe	cag Gln	Ala	gag Glu 1020	ggc Gly	gat Asp	gcc Ala	aac Asn	3072
40	aga Arg 102	Ser	gac Asp	acg Thr	gac Asp	gag Glu 1030	gac Asp	aag Lys	acg Thr	Ser	gtc Val 1035	cac His	ttc Phe	gag Glu	Glu	gac Asp 1040	3120
45	ttc Phe	cac His	aag Lys	Leu	aga Arg 1045	gaa Glu	ctc Leu	cag Gln	Thr	aca Thr 1050	gag Glu	ctg Leu	aag Lys	Met	tgt Cys 1055	tcc Ser	3168
50	ctg Leu	gcc Ala	Val	acc Thr 1060	ccc	aac Asn	ggc Gly	Thr	tgg Trp 1065	agg Arg	gac Asp	gag Glu	Ala	gcc Ala 1070	tgt Cys	ccc Pro	3216 · .
50	ctc Leu	Pro	tca Ser 1075	tca Ser	tgt Cys	gca Ala	Gln	ctg Leu 1080	cca Pro	cgc Arg	cca Pro	Cys	cta Leu 1085	ccc Pro	CCa Pro	aga Arg	3264
55	Ala	cac His 1090	His	tcc Ser	tgg Trp	Met	cag Gln 1095	ccc Pro	cca Pro	gcc Ala	Ser	cag Gln 1100	act Thr	ctc Leu	ggc Gly	gtg Val	3312
60	gca Ala 110	Ala	gca Ala	gct Ala	ccg Pro	ggg Gly 1110	acc Thr	cgc Arg	cac His	Trp	gag Glu 1115	acc Thr	aga Arg	agc Ser	Leu	cgg Arg 1120	3360
	cag Gln	cct Pro	ccg Pro	aag Lys	ttc Phe	tcc Ser	ctg Leu	tgc Cys	ccc Pro	ctg Leu	ggg Gly	ccc Pro	agt Ser	ggc Gly	gcc Ala	tgg Trp	3408

	1125	1130	1135
5	age age egg ege tee age tegg	age age etg gge egt (gcc cag cct caa 3456
	Ser Ser Arg Arg Ser Ser Trp :	Ser Ser Leu Gly Arg)	Ala Gln Pro Gln
	1140	1145	1150
10	gog cog gog tgo cag tgo ggg d Ala Pro Ala Cys Gln Cys Gly (1155	olu Arg Glu Ser Leu I	ctg tot ggc gag 3504 Leu Ser Gly Glu 165
·	ggc aag ggc agc acc gac gac g Gly Lys Gly Ser Thr Asp Asp C 1170	gaa gct gag gac ggc a Glu Ala Glu Asp Gly A 1180	egg gcg cgc tcc 3552 erg Ala Arg Ser
15	ggg ccc cgt gcc acc cca ctg c Gly Pro Arg Ala Thr Pro Leu A 1185 1190	ogg ogg god gag tod o Arg Arg Ala Glu Ser I 1195	eu Asp Pro Arg 1200
20	ccc ctg cgg cgg ccg cct ccc g	cc tac caa gtg cgc g	at cgc gac ggg 3648
	Pro Leu Arg Arg Pro Pro Pro A	la Tyr Gln Val Arg A	sp Arg Asp Gly
	1205	1210	1215
25	cag gtg gtg gcc ctg ccc agc g	ac ttc ttc ctg cgc a	to gad ago dad 3696
	Gln Val Val Ala Leu Pro Ser A	sp Phe Phe Leu Arg I	le Asp Ser His
	1220	1225	1230
30	cgt gag gat gca gcc gag ctt g Arg Glu Asp Ala Ala Glu Leu A 1235 12	sp Asp Asp Ser Glu A	sp Ser Cys Cys
	ctc cgc ctg cat aaa gtg ctg gt Leu Arg Leu His Lys Val Leu Va 1250 1255	tg ccc tac aag ccc ca al Pro Tyr Lys Pro G 1260	ag cgg tgc cgg 3792 Ln Arg Cys Arg
35	agc agg agg cct ggg ccc tct ac	cc ctc tac ctc ttc to	cc cca cag aac 3840
	Ser Arg Arg Pro Gly Pro Ser Th	or Leu Tyr Leu Phe Se	er Pro Gln Asn
	1265 1270	1275	1280
40	cgg ttc cgc gtc tcc tgc cag as	ag gtc atc aca cac aa	g atg ttt gat 3888
	Arg Phe Arg Val Ser Cys Gln Ly	/s Val Ile Thr His Ly	s Met Phe Asp
	1285	1290	1295
45	cac gtg gtc ctc gtc ttc atc tt	c ctc aac tgc gtc ac	c atc gcc ctg 3936
	His Val Val Leu Val Phe Ile Ph	ne Leu Asn Cys Val Th	r Ile Ala Leu
	1300	1305	1310
<i>50</i>	gag agg cct gac att gat ccc gg Glu Arg Pro Asp Ile Asp Pro Gl 1315	y Ser Thr Glu Arg Va	l Phe Leu Ser
	gtc tcc aat tac atc ttc acg gc Val Ser Asn Tyr Ile Phe Thr Al 1330	c atc ttc gtg gcg ga a Ile Phe Val Ala Gl 1340	g atg atg gtg 4032 u Met Met Val
<i>55</i>	aag gtg gtg gcc ctg ggg ctg ctc	g too ggo gag cac go	c tac ctg cag 4080
	Lys Val Val Ala Leu Gly Leu Leu	u Ser Gly Glu His Ala	a Tyr Leu Gln
	1345	1355	1360
60	agc agc tgg aac ctg ctg gat ggg	g ctg ctg gtg ctg gtg	g too otg gtg 4128
	Ser Ser Trp Asn Leu Leu Asp Gly	y Leu Leu Val Leu Val	l Ser Leu Val
	1365	1370	1375
	gac att gtc gtg gcc atg gcc tcc	g gct ggt ggc gcc aag	g atc ctg ggt 4176
	Asp Ile Val Val Ala Met Ala Ser	c Ala Gly Gly Ala Lys	s Ile Leu Gly

	1380		1385	1390	
5	gtt ctg cgc gtg Val Leu Arg Val 1395	Leu Arg Leu	ctg cgg acc Leu Arg Thr 400	ctg cgg cot ctg Leu Arg Pro Leu 1405	agg gtc 4224 Arg Val
	atc agc cgg gcc Ile Ser Arg Ala 1410	ccg ggc ctc Pro Gly Leu 1415	aag ctg gtg Lys Leu Val	gtg gag acg ctg Val Glu Thr Leu 1420	ata tca 4272 Ile Ser
10	tca ctc agg ccc Ser Leu Arg Pro 1425	att ggg aac lle Gly Asn 1430	Ile Val Leu	atc tgc tgc gcc Ile Cys Cys Ala 435	ttc ttc 4320 Phe Phe 1440
15	atc att ttt ggc Ile Ile Phe Gly	att ttg ggt Ile Leu Gly 1445	gtg cag ctc Val Gln Leu 1450	ttc aaa ggg aag Phe Lys Gly Lys 1	ttc tac 4368 Phe Tyr . 455
20	tac tgc gag ggc Tyr Cys Glu Gly 1460	Pro Asp Thr	agg aac atc Arg Asn Ile 1465	tcc acc aag gca Ser Thr Lys Ala 1470	cag tgc 4416 Gln Cys
25	cgg gcc gcc cac Arg Ala Ala His 1475	Tyr Arg Trp	gtg cga cgc Val Arg Arg 1480	aag tac aac ttc Lys Tyr Asn Phe 1485	gac aac 4464 Asp Asn
20	ctg ggc cag gcc Leu Gly Gln Ala 1490	ctg atg tcg Leu Met Ser 1495	ctg ttc gtg Leu Phe Val	ctg tca tcc aag Leu Ser Ser Lys 1500	gat gga 4512 Asp Gly
30	tgg gtg aac ato Trp Val Asn Ile 1505	atg tac gac Met Tyr Asp 1510	Gly Leu Asp	gcc gtg ggt gtc Ala Val Gly Val 515	gac cag 4560 Asp Gln 1520
35	cag cct gtg cag Gln Pro Val Glr	g aac cac aac n Asn His Asn 1525	ccc tgg atg Pro Trp Met 1530	ctg ctg tac ttc Leu Leu Tyr Phe	atc tcc 4608 Ile Ser 1535
40	ttc ctg ctc atc Phe Leu Leu Ile 1540	e Val Ser Phe	ttc gtg ctc Phe Val Leu 1545	aac atg ttc gtg Asn Met Phe Val 1550	ggc gtc 4656 Gly Val
45	gtg gtc gag aad Val Val Glu Ass 1555	n Phe His Lys	tgc cgg ccg Cys Arg Pro 1560	cac cag gag gcg His Gln Glu Ala 1565	gag gag 4704 Glu Glu
50	gcg cgg cgg cg Ala Arg Arg Ar 1570	a gag gag aag g Glu Glu Lys 1575	cgg ctg cgg Arg Leu Arg	cgc cta gag agg Arg Leu Glu Arg 1580	agg cgc 4752 Arg Arg
50	agg agc act tt Arg Ser Thr Ph 1585	c ccc agc cca e Pro Ser Pro 1590	Glu Ala Gln	cgc cgg ccc tac Arg Arg Pro Tyr 1595	tat gcc 4800 Tyr Ala 1600
55	gac tac tcg cc Asp Tyr Ser Pr	c acg cgc cgc o Thr Arg Arg 1605	tgg att cac Trp Ile His 1610	tcg ctg tgc acc Ser Leu Cys Thr	agc cac 4848 Ser His 1615
60	tat ctc gac ct Tyr Leu Asp Le 162	u Phe Ile Thr	ttc atc atc Phe Ile Ile 1625	tgt gtc aac gtc Cys Val Asn Val 1630	Tie int
	atg tcc atg ga Met Ser Met Gl	g cac tat aac u His Tyr Asn	caa ccc aag Gln Pro Lys	tcg ctg gac gag Ser Leu Asp Glu	gcc ctc 4944 Ala Leu

	1635	1640	1645	
5	aag tac tgc aac tac Lys Tyr Cys Asn Tyr 1650	gto tto acc atc gtg Val Phe Thr Ile Val 1655	ttt gtc ttc gag gct gca Phe Val Phe Glu Ala Ala 1660	4992
10	100 2/0 Edd val Kid	and Gry and Wad	tto tto aag gao agg tgg Phe Phe Lys Asp Arg Trp 1675 1680	5040
	aac cag ctg gac ctg Asn Gln Leu Asp Leu 1685	gcc atc gtg ctg ctg Ala Ile Val Leu Leu 1690	tca ctc atg ggc atc acg Ser Leu Met Gly Ile Thr 1695	5088
15	ctg gag gag ata gag Leu Glu Glu Ile Glu 1700	atg agc gcc gcg ctg Met Ser Ala Ala Leu 1705	ccc atc aac ccc acc atc Pro Ile Asn Pro Thr Ile 1710	5136
20	atc cgc atc atg cgc Ile Arg Ile Met Arg 1715	gtg ctt cgc att gcc Val Leu Arg Ile Ala 1720	cgt gtg ctg aag ctg ctg Arg Val Leu Lys Leu Leu 1725	5184
25	aag atg gct acg ggc Lys Met Ala Thr Gly 1730	atg cgc gcc ctg ctg Met Arg Ala Leu Leu 1735	gac act gtg gtg caa gct Asp Thr Val Val Gln Ala 1740	5232
30	acq 110 GIN val Gly	Asn Leu Gly Leu Leu	ttc atg ctc ctg ttt ttt Phe Met Leu Leu Phe Phe 755	5280
	atc tat gct gcg ctg (Ile Tyr Ala Ala Leu (1765	gga gtg gag ctg ttc Gly Val Glu Leu Phe 1770	ggg agg ctg gag tgc agt Gly Arg Leu Glu Cys Ser 1775	5328
35	gaa gac aac ccc tgc o Glu Asp Asn Pro Cys (1780	gag ggc ctg agc agg o Glu Gly Leu Ser Arg 1 1785	cac gcc acc ttc agc aac His Ala Thr Phe Ser Asn 1790	5376
40	ttc ggc atg gcc ttc c Phe Gly Met Ala Phe I 1795	etc acg ctg ttc cgc of Leu Thr Leu Phe Arg (1800	gtg tcc acg ggg gac aac Val Ser Thr Gly Asp Asn 1805	5424
45	tgg aac ggg atc atg a Trp Asn Gly Ile Met I 1810	ag gac acg ctg cgc o ys Asp Thr Leu Arg o 1815	gag tgc tcc cgt gag gac Glu Cys Ser Arg Glu Asp 1820	5472
50	~10 "TO CAP Den Del I	yr Leu Pro Ala Pro S	Ser Pro Val Tyr Phe Val	5520
	acc ttc gtg ctg gtg c Thr Phe Val Leu Val P 1845	cc cag ttc gtg ctg g ro Gln Phe Val Leu V 1850	gtg aac gtg gtg gcc Val Asn Val Val Val Ala 1855	5568
	gtg ctc atg aag cac c Val Leu Met Lys His L 1860	tg gag gag agc aac a eu Glu Glu Ser Asn L 1865	lag gag get egg gag gat Lys Glu Ala Arg Glu Asp 1870	5616
60	gcg gag ctg gac gcc ga Ala Glu Leu Asp Ala G 1875	ag atc gag ctg gag a lu Ile Glu Leu Glu M 1980	tg gcg cag ggc ccc ggg et Ala Gln Gly Pro Gly 1885	5664
	agt gca cgc cgg gtg ga Ser Ala Arg Arg Val As	ac geg gac agg cet co sp Ala Asp Arg Pro P	cc ttg ccc cag gag agt ro Leu Pro Gin Glu Ser	5 7 12

	1890	1	895	1	900	
<i>5</i>	ccg ggs gss a Pro Gly Ala A 1905	gg gac gcc rg Asp Ala 1910	cca aac c Pro Asn L	etg gtt gca e eu Val Ala . 1915	ogo aag gtg to Arg Lys Val Se	cc gtg 5760 er Val 1920
10	toc aggratg c Ser Arg Met L	to tog ctg eu Ser Leu 1925	ccc aac g Pro Asn A	ac ago tac sp Ser Tyr (atg tto agg co Met Phe Arg Pr 193	o Val
10	Val Pro Ala S	cg gcg ccc er Ala Pro 40	cac ccc c His Pro A 19	rg Pro Leu (cag gag gtg ga Gln Glu Val Gl 1950	ag atg 5856 .u Met
15	gag acc tat g Glu Thr Tyr G 1955	gg gcc ggc ly Ala Gly	acc ccc to Thr Pro Lo 1960	tg ggc tcc (eu Gly Ser	gtt gcc tct gt Val Ala Ser Va 1965	g cac 5904 al His
20	tct ccg ccc g Ser Pro Pro A 1970	la Glu Ser	tgt gcc to Cys Ala So 975	er Leu Gln	atc cca ctg go Ile Pro Leu Al 980	t gtg 5952 a Val
25	tcg tcc cca g Ser Ser Pro A 1985 .	cc agg agc la Arg Ser 1990	ggc gag co Gly Glu P	cc ctc cac or to Leu His 1	gcc ctg tcc co Ala Leu Ser Pr	ct cgg 6000 co Arg 2000
<i>30</i>	ggc aca gcc c Gly Thr Ala A	gc tcc ccc rg Ser Pro 2005	agt ctc ad Ser Leu S	gc cgg ctg er Arg Leu : 2010	ctc tgc aga ca Leu Cys Arg Gl 201	.n Glu
	Ala Val His T	cc gat tcc hr Asp Ser 20	ttg aag g Leu Lys G 20	ly Arg Leu '	aca gcc cta gg Thr Ala Leu Gl 2030	gg aca 6096 y Thr
35	ccc tgg atc c Pro Trp Ile L 2035	tg cag agc eu Gln Ser	ctg gtg a Leu Val A 2040	ga aaa ccc rg Lys Pro	cgg Arg	6132
40	<210> 10 <211> 6114 <212> DNA <213> Homo sa	piens				
45	<220> <221> CDS <222> (1)(6	114)				
50	<400> 10 atg acc gag g Met Thr Glu G 1	gc gca cgg ly Ala Arg S	gcc gcc g Ala Ala A	ac gag gtc : sp Glu Val : 10	cgg gtg ccc ct Arg Val Pro Le	g ggg 48 eu Gly
<i>55</i>	cgc cgc ccc t Arg Arg Pro T	gg ccc tgc rp Pro Cys 20	Gly Val G	ggt ggg ggc Gly Gly Gly 25	gtc ccc gga ga Val Pro Gly Gl 30	ag ccc 96 Lu Pro
60	cgg ggc gcc g Arg Gly Ala G 35	gg acg cga Sly Thr Arg	ggc gga g Gly Gly G 40	ggg ggg ttc Gly Phe	gag ctc ggc g Glu Leu Gly V 45	ig toa 144 al Ser
	ccc tcc gag a Pro Ser Glu S 50	igc ccg gcg Ser Pro Ala	gcc gag c Ala Glu A 55	gc tgc gcg Arg Cys Ala	gag ctg ggt go Glu Leu Gly A 60	cc gac 192 la Asp

5	6	5			go ga rg Va	7	70	Yr P.	20 A	la L	.eu	75	a Al	a Ti	ır V	al P	he	Phe 80	240
	t go Cys	c ct s Le	ic gg	gt ca .y Gl	ag ac In Th	c ac r Th	g co ar Ar	gg co	eg c co A	gc a rg S	gc er 90	tgg Trp	tg Cy	c ct s Le	io co su Ai	g L	cg eu 95	gtc Val	288
10	t go Cys	aa As	c cc n Pr	a to o Tr 10	ig tt p Ph 0	c ga e Gl	g ca u Hi	ic gt .s Va	1 2	gc a er M 05	tg et	ctg	gt. Va	a at 1 Il	c at e Me 11	t Le	tc eu	aac Asn	336
15	t go Cys	gt Va	g ac l Th ll		g gg u Gl	c at y Me	g tt t Ph	c cg e Ar 12	g Pi	co to	gt ys (gag Glu	gad Asg	= gt Va 12	l Gl	g to u Cy	JC /S	ggc Gly	384
20	tcc Ser	ga Gl: 130		c tg g Cy	c aa s As:	c ato	c cto e Les 13	a GI	g go u Al	c t: .a Pl	tt d	gac Asp	gcc Ala 140	Ph:	c at e Il	t tt e Ph	c ie	gcc Ala	432
25	ttt Phe 145	tt: Phe	t gco ∋ Ala	g gte a Val	g gác l Gli	g ato 1 Met 150	- va.	c at	c aa e Ly	g at	ים ע	gtg /al l55	gcc Ala	tt: Le:	ı Gl	g ct y Le	u	ttc Phe 160	480
	G] À ààà	Glr	g aaq n Lys	g tgt s Cys	t tac 5 Ty: 165	. 100	g ggt ı Gly	gad Ası	c ac	g tg r Tr 17	ρA	aac Asn	agg Arg	cto Leu	g ga: 1 As _l	t tt Ph 17	e :	ttc Phe	528
30	atc Ile	gtc Val	gto Val	g gcg Ala 180	g ggc a Gly	atg Met	atg Met	g gaq Glu	y ta 1 Ty 18	r Se	g t r L	tg .eu	gac Asp	Gly	cad His	As	u /	gtg Val	576
35	agc Ser	ctc Leu	Ser 195	VIO	atc Ile	agg Arg	acc Thr	gtg Val 200	Are	g gt g Va	g c l L	tg eu	cgg Arg	ecc Pro 205	Leu	cgo Aro	e e	gcc Ala	624
40		210	**-9	Val	cct Pro	Set	215	Arg	116	. Le	u V	al :	Thr 220	Leu	Leu	Leu	1 A	usp	672
45	225			nec	ctc Leu	230	ASII	vai	rec	ı Let	1 Le	eu (35	Cys	Phe	Phe	Val	. P	he 40	720
	ttc . Phe	att Ile	ttc Phe	Gly	atc Ile 245	gtt Val	ggc Gly	gtc Val	cag Gln	Leu 250	l Tr	sp A	gct Ala	ggc Gly	ctc Leu	ctg Leu 255	Α	gg rg	768
50	aac (Asn <i>i</i>	cgc Arg	tgc Cys	ttc Phe 260	ctg Leu	gac Asp	agt Ser	gcc Ala	ttt Phe 265	gtc Val	aç Ar	ig A	aac Asn	aac Asn	aac Asn 270	ctg Leu	a Ti	ee hr	816
<i>55</i>	ttc o	ctg Leu	cgg Arg 275	ccg Pro	tac Tyr	tac Tyr	cag Gln	acg Thr 280	gag Glu	gag Glu	gg Gl	y G	ilu	gag Glu 285	aac Asn	ccg Pro	t i	tc ne	864
60	atc t Ile C	gc Cys 290	tcc Ser	tca Ser	cgc Arg	Ar 9	gac Asp 295	aac Asn	ggc Gly	atg Met	ca Gl	n L	ag ys (tgc Cys	tcg Ser	cac His	at Il	ic le	912
	ccc g Pro G 305	igc Hy	cgc Arg	cgc Arg	gac Asp	gtg Val 310	ege Arg	atg Met	ccc Pro	tgc Cys	ac Th 31	r L	tg (ggc Gly	tgg Trp	gag Glu	gc A1 32	.a	960

5											gct Ala						1003
,											cgc Arg						1056
10	ccc Pro	cac His	aac Asn 355	ggt Gly	gcc Ala	atc Ile	aac Asn	ttc Phe 360	gac Asp	aac Asn	acc Thr	tgc Cys	tac Tyr 365	gcc Ala	tgg Trp	att Ile	1104
15	gcc Ala	atc Ile 370	ttc Phe	cag Gln	gtg Val	atc Ile	acg Thr 375	ctg Leu	gaa Glu	ggc Gly	tgg Trp	gtg Val 380	gac Asp	atc Ile	atg Met	tac Tyr	1152
20											ttc Phe 395						1200
25	ctc Leu	atc Ile	atc Ile	gtg Val	ggc Gly 405	tcc Ser	ttc Phe	ttc Phe	atg Met	atc Ile 410	aac Asn	ctg Leu	tgc Cys	ctg Leu	gtg Val 415	gtg Val	1248
23											cgg Arg						1296
30											gac Asp						1344
35	ttc Phe	tcc Ser 450	gag Glu	cct Pro	ggc Gly	agc Ser	tgc Cys 455	tac Tyr	gaa Glu	gag Glu	ctg Leu	ctg Leu 460	aag Lys	tac Tyr	gtg Val	ggc Gly	1392
40	cac His 465	ata Ile	ttc Phe	cgc Arg	aag Lys	gtc Val 470	aag Lys	cgg Arg	cgc Arg	agc Ser	ttg Leu 475	cgc Arg	ctc Leu	tac Tyr	gcc Ala	cgc Arg 480	1440
45											ccc Pro						1488
73											ggc Gly						1536
50	gtg Val	cac His	cac His 515	ctg Leu	gtc Val	tac Tyr	cac His	cac His 520	cat His	cac His	cac His	cac His	cac His 525	cac His	cac His	tac Tyr	1584
55	cat His	ttc Phe 530	agc Ser	cat His	ggc Gly	agc Ser	ccc Pro 535	cgc Arg	agg Arg	ccc Pro	ggc Gly	ccc Pro 540	gag Glu	cca Pro	ggc Gly	gcc Ala	1632
60	tgc Cys 545	gac Asp	acc Thr	agg Arg	ctg Leu	gtc Val 550	cga Arg	gct Ala	ggc Gly	gcg Ala	ccc Pro 555	ccc Pro	tcg Ser	cca Pro	cct Pro	tcc Ser 560	1680
	cca Pro	ggc Gly	cgc Arg	gga Gly	ccc Pro 565	ccc Pro	gac Asp	gca Ala	gag Glu	tct Ser 570	gtg Val	cac His	agc Ser	atc Ile	tac Tyr 575	cat His	1728

5			•	5	80		ag g lu G	-y .	10	585		u A	rg /	A⊥a	Arq	y Va 59	l G	ly	Thr	
	_		5 9	95	-5 0	,	gc t rg C	6	00	210	61	n A,	la (эŁУ	His	Ar	g A.	la	Gly	1824
10	Hi	61	0					15	_0 /	n.i.a	re	ı Ai	rg 6	120 20	Gly	Gl	n Ar	g	Gln	1872
15	625	5				6.			٠ ر	3 ± Y	GI	63	11 G	тÀ	Arg	Trį	o Th	r	Ala 640	1920
20	-			,	64	5	je ec y Pr	0 1.6	eu S) = I	650	AS	n S	er :	Pro	Asp	Pr 65	o 5	Tyr	1968
25		-		66	0		g gc l Al	u ():	.y G	65	nis	GT.	у г	∋u (Sly	Gln 670	Al.	a .	Pro	2016
30	_		675	5		, 110	c ag u Se	68	0	10	cys	Pro	э ге	eu E	85 85	Ser	Pro	o 1	Pro	2064
30		690)		- 1	- Су.	t gad s Glu 699	5	a ri	ys .	ser	Cys	70	0 T	'yr	Cys	Thi	: <i>F</i>	Arg	2112
35	705				, , ,	710		/ GI	بل ابو	eu :	ser	G15 715	y Se	r G	lu	Ser	Gly	7. 7	sp 20	2160
40			,	- •- 9	725	* 44.1	tat Tyr	GI	1 50	ie i	730	GIn	As	p V.	al A	Arg	His 735	G	ly	2208
45	•	5		740	1.0	1111		FIC	74	5 A	irg	Ala ,	Th:	r As	ds de	Thr 750	Pro	G	lу	2256
50	cca Pro	4	755			110	OIII	760	Ai	y A	та (GIN	Glr	1 Ar 76	rg <i>P</i> 55	Ala	Ala	P	ro	2304
50		770		U	115	.120	775	Arg	ьe	u i	rp '	val	780	Ph	ie S	er	Gly	L١	/S	2352
<i>55</i>	Leu 2 785		9			790	Ser	μÃ2	ı yı		ne s	95 795	Arg	G1	уI	le :	Met	M∈ 80	et O	2400
<i>60</i> .	gcc a				805	****	Deu	261	net	81	10 V	/al	GLu	Тy	r H	is (31u 315	Gl	.n	2448
	Pro C	gag Slu		ctg Leu 820	act Thr	aat Asn	gct Ala	ctg Leu	gaç Glu 325	1 11	c a le S	gc	aac Asn	at: Il:	e Va	tg 1 al 1 30	tc Phe	ac Th	c r	2496

5	agc Ser	atg Met	ttt Phe 835	Ala	ctg Leu	gaş Glu	atg Met	ctg Leu 840	Leu	aag Lys	cto Lei	j cto	gco Ala 845	Cys	gg: Gl:	y Pro	2544
	ctg Leu	ggc Gly 850	Tyr	atc Ile	cgg Arg	aac Asn	ecg Pro 855	tac Tyr	aac Asn	atc Ile	tto Phe	gac Asp 860	Gly	al:	ato Ele	e gtg	2592
10	gtc Val 865	atc Ile	agc Ser	gtc Val	tgg Trp	gag Glu 870	atc Ile	gtg Val	GJ À dad	cag Gln	gcg Ala 875	Asp	Gly	ggs Gly	tto Leu	g tot Ser 880	2640
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25	aac Asn	gtg Val	gct Ala 915	acc Thr	ttc Phe	tgc Cys	acg Thr	ctg Leu 920	ctc Leu	atg Met	ctc Leu	ttc Phe	att Ile 925	ttc Phe	atc Ile	ttc Phe	2784
	agc Ser	atc Ile 930	ctg Leu	ggc Gly	atg Met	cac His	ctt Leu 935	ttc Phe	ggc Gly	tgc Cys	aag Lys	ttc Phe 940	agc Ser	ctg Leu	aag Lys	aca Thr	2832
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	Leu	gtg Val 010	gcc Ala	atc Ile	ctc Leu	Val	gag Glu 015	ggc Gly	ttc Phe	cag Gln	Ala	gag Glu .020	ggc Gly	gat Asp	gcc Ala	aac Asn	3072
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	ctc Leu	Pro	tca Ser 075	tca Ser	tgt Cys	gca (Ala (Gln :	ctg Leu 080	cca (Pro 1	cgc (Arg)	cca Pro	Cys	cta Leu 035	ccc Pro	cca Pro	aga Arg	3264

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15	1140 Ser Ser Leu Gly Arg Ala Gln Pro Gln 1145 1150	3456
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30	1205 1210 Ala Tyr Gin Val Arg Asp Arg Asp Gly	3648
35	1220 1225 Leu Arg Ile Asp Ser His	3696
40	1235 1:240 Asp Asp Ser Glu Asp Ser Cys Cys	3744
45	1250 1255 Tyr Lys Pro Gln Arg Cys Arg	3792
50	1265 1270 1275 Leu Phe Ser Pro Gln Asn 1275 1280	3840
50	1295 1290 1295	8888
55	1300 land tall the life Phe Leu Asn Cys Val Thr Ile Ala Leu	936
60	1315 1320 Ser Thr Glu Arg Val Phe Leu Ser	984
	yal Ser Asn Tyr Ile Phe Thr Ala Ile Phe Val Ala Glu Met Met Val 1330 1335 1340	032

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15	gtt ctg Val Leu	cgc Arg 1395	gtg Val	ctg Leu	cgt Arg	Leu	ctg Leu 1400	Arg	acc Thr	ctg Leu	Arg	ect Pro 405	ctg Leu	agg Arg	gtc Val	4224
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40	ctg ggc Leu Gly 1490	cag Gln	gcc Ala	ctg Leu	Met	tcg Ser 1495	ctg Leu	ttc Phe	gtg Val	Leu	tca Ser 500	tcc Ser	aag Lys	gat Asp	gga Gly	4512
45	tgg gtg Trp Val 1505	Asn	Ile	Met	Tvr	Asp	Gly	Leu	Asp	Ala	Val	Gly	Val	Asp	Gln	4560
,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	cag cct Gln Pro	gtg Val	Gln	aac Asn 1525	cac His	aac Asn	ccc Pro	Trp	atg Met 1530	ctg Leu	ctg Leu	tac Tyr	Phe	atc Ile 1535	tcc Ser	4608
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	agg aag Arg Lys 1585	gcc Ala	cag Gln	Arg	cgg Arg 1590	ccc Pro	tac Tyr	tat Tyr	Ala	gac Asp 1595	tac Tyr	tcg Ser	ccc Pro	Thr	cgc Arg 1600	4800

<i>5</i>	cgc tgg att cac tcg ctg tgc acc age cac tat ctc gac ctc ttc atc Arg Trp Ile His Ser Leu Cys Thr Ser His Tyr Leu Asp Leu Phe Ile 1605 1610	4848
	acc ttc atc atc tgt gtc aac gtc atc acc atg tcc atg gag cac tat Thr Phe Ile Ile Cys Val Asn Val Ile Thr Met Ser Met Glu His Tyr 1620 1630	4896
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15	ttc acc atc gtg ttt gtc ttc gag gct gca ctg aag ctg gta gca ttt Phe Thr Ile Val Phe Val Phe Glu Ala Ala Leu Lys Leu Val Ala Phe 1650 1650	4992
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25	atc gtg ctg ctg tca ctc atg ggc atc acg ctg gag gag ata gag atg Ile Val Leu Leu Ser Leu Met Gly Ile Thr Leu Glu Glu Ile Glu Met 1685 1690 1695	5088
	age gee geg etg eee ate aac eee aee ate ate ege ate atg ege gtg Ser Ala Ala Leu Pro Ile Asn Pro Thr Ile Ile Arg Ile Met Arg Val 1700 1705 1710	5136
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50	acg ctg ttc cgc gtg tcc acg ggg gac aac tgg aac ggg atc atg aag Thr Leu Phe Arg Val Ser Thr Gly Asp Asn Trp Asn Gly Ile Met Lys 1795 1800 1805	5424
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	Cag ttc gtg ctg gtg aac gtg gtg gtc gtg ctc atg aag cac ctg Gln Phe Val Leu Val Asn Val Val Val Ala Val Leu Met Lys His Leu 1845 1850 1855	5568

ĵ	gag gag agt aac aag gag got ogg gag gat gog gag otg gac goo gag Glu Glu Ser Asn Lys Glu Ala Arg Glu Asp Ala Glu Leu Asp Ala Glu 1860 . 1365 1870	5616
	atc gag ctg gag atg gcg cag ggc ccc ggg agt gca cgc cgg gtg gac Ile Glu Leu Glu Met Ala Gln Gly Pro Gly Ser Ala Arg Arg Val Asp 1875 1889 1885	5664
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55	<213> Homo sapiens <220> <221> CDS	٠
60	<222> (1)(5469)	
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. 5		o to r Se		og co o Pr	ca gg co Gl	c ct y Le	g ga u Gl	g ga u Gl 4	4 ZZ	t ct o Le	g ga u As _i	t gg: p Gl:	a go y Al. 4	a As	t co p Pr	cat co His	144
10	_	5	0	5 . 1	O AS	b re	u A1.	a Pro 5	0 11	e Ala	a Phe	Ph∈ 60	e Cys	s Le	u Ar	ra cag g Gln	192
15	6	5				7	0	. Cys	2 1.16	: Lys	75 75	val	. Cys	s As:	n Pr	g tgg o Trp 80	240
20			ш Су	J V G	85	. Me	r ne:	l Val	- 1 1 6	90 90	. Leu	ı Asn	Cys	Val	l Th 9		288
	,	•••	- 1 y	10	0	, су	y WSE	Asp	105	Asp	Cys	Leu	Ser	Asr 110	Aro	c tgc g Cys	336
25	-,-	\	119	5	ı vaı	FILE	: Asp	120	. sue	lle	Phe	Ile	Phe 125	Phe	Alá	atg Met	384
30		130			. 233	- 1100	135	AIG	Leu	GIY	rre	140	GIY	Lys	Lys	g tgc G Cys	432
35	145	200	. 01.	, voř	, 1111	150	ASII	Arg	Leu	Asp	Phe 155	Phe	Ile	Val	Met	gca Ala 160	480
40	01,		va1	GIU	tac Tyr 165	Ser	Leu	Asp	Leu	170	Asn	Ile	Asn	Leu	Ser 175	Ala	528
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	tac Tyr	cag Gln	ccg Pro	gag Glu 260	gag Glu	gat Asp	gat (Asp (eru :	atg Met 1 265	ecc i	ttc a Phe :	atc 1 Ile (Cys :	tcc Ser 270	ctg Leu	tcg Ser	816

												ccc Pro		Leu			864
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25	gct Ala	cac His 370	tcc Ser	ttc Phe	tac Tyr	aac Asn	ttc Phe 375	atc Ile	tac Tyr	ttc Phe	atc ·Ile	ctg Leu 380	ctt Leu	atc Ile	ata Ile	gtg Val	1152
30	ggc Gly 385	tcc Ser	ttc Phe	ttc Phe	atg Met	atc Ile 390	aac Asn	ctg Leu	tgc Cys	ctc Leu	gtt Val 395	gtc Val	ata Ile	gcg Ala	Thr	cag Gln 400	1200
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	tcc Ser	gat Asp	ccc Pro 515	gcc Ala	agc Ser	tgc Cys	cct Pro	tgc Cys 520	tgc Cys	cag Gln	cat	gag Glu	gac Asp 525	ggc Gly	cgg Arg	Arg	1584

	00 P1	5 56 5 53		go ot .y Le	g gg u Gl	o ag y Se	c ac r Th 53	1 25	c to p Se	g gg r Gl	ca y Gl	g ga n Gl 54	u Gi	s to 7 Se	g gg r Gl	ic tee y Ser	1632
5	54	5		- AI	a G1	550) A GI	u AS	b GI	u Ali	5.5	p Gl 5	y As	p G1	y Al	c cgg a Arg 560	1680
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15	Q1.	. 01	u <u>G</u> 1	580	a Asi	b GIŽ	/ Ala	a va.	585	o Leu	: Cys	s Gl	/ Asp	590	l Tri	g cgg o Arg	1776
20	010		59!	2 2	a rās	s ren	Arc	600) ∖ ;⊺€	e Val	Asr) Ser	Lys 605	Tyr	Phe	aac Asn	1824
	agg Arg	Gly 610	,	e Met	g ato Met	g gcc : Ala	ato Ile 615	: шел	gto Val	aac Asn	acc Thr	gtc Val 620	Ser	atç Met	Gly Gly	atc Ile	1872
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	ttc Phe	gac Asp 770	tcc Ser	ctg Leu	ctg Leu	TED.	gcc Ala 775	atc Ile	gtc . Val '	act o	Val	ttc Phe 780	cag (Gln)	atc Ile	ctc Leu	ace Thr	2352

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_	Aid his	e Pro Arc	1045	a Trp Ar	g Ala Ala 1050		ia Pro Gly 105	y His 5
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10	<220 <221	> > C[·									··	
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20	gag Glu	ccg Pro	gga Gly	atc Ile 20	act Thr	gag Glu	cag Gln	ccg Pro	ggg Gly 25	ccc Pro	cgg Arg	agt Ser	Pro CCC	cct Pro 30	cca Pro	tcc Ser	96
25	cct Pro	cca Pro	ggc Gly 35	ctg Leu	gag Glu	gag Glu	cca Pro	ttg Leu 40	gaa Glu	gga Gly	acc Thr	aac Asn	cct Pro 45	gac Asp	gtc Val	cca Pro	144
30	cat His	cca Pro 50	gac Asp	ctg Leu	gct Ala	CCT Pro	gtt Val 55	gct Ala	ttc Phe	ttc Phe	tgc Cys	ctg Leu 60	cgc Arg	cag Gln	acc Thr	acg Thr .	192
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	tgt Cys	gtg Val	agc Ser	atg Met	ctg Leu 85	gtt Val	att Ile	ctg Leu	ctg Leu	aac Asn 90	tgt Cys	gtg Val	acc Thr	ctg Leu	ggc Gly 95	atg Met	288
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	gtt Val	gag Glu	tac Tyr	tct Ser	ctg Leu 165	gac Asp	cta Leu	cag Gln	aac Asn	atc Ile 170	aac Asn	ctg Leu	tca Ser	gcc Ala	atc Ile 175	cgc Arg	528
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	aac Asn	ttt Phe	gac Asp	aac Asn 340	att Ile	ggc Gly	tat Tyr	gcc Ala	999 Gly 345	att Ile	gtg Val	att Ile	ttc Phe	cag Gln 350	gtg Val	atc Ile	1056
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	Al 70	.a Le 15	eu Ai	ig Ai	rg Gl	.n Le 7]	eu Va 10	il Va	el Le	∋u Me	et Ly 7:	/s Tr l5	er M	et A.	sp A:	sn Val 720	
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	cgg Arg	agc Ser 930	tcc Ser	tac Tyr	tac Tyr	ggg Gly	ccc Pro 935	tgg Trp	ggc Gly	cgc Arg	agt Ser	999 Gly 940	acc Thr	tgg Trp	gct Ala	agc Ser	2832
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	cat	gag	tcc	tta	ctg	tct	9 99	gaş	ggt	gga	ggt	agc	tgc	gtc	agg	gee	2928

												T					
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<i>==</i>	Ile	ttc Phe 170	aca Thr	gcc Ala	atc Ile	Phe	gtg Val 1175	ggc Gly	gag Glu	atg Met	Thr	ctg Leu 1180	aag Lys	gtg Val	gtt Val	tct Ser	3552
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	atc ctg ggg gtg cag ctt ttc aaa ggc aag ttc tac cat tgt ttg gga Ile Leu Gly Val Gln Leu Phe Lys Gly Lys Phe Tyr His Cys Leu Gly 1285 1290 1295	3888
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15	tcc gtc Ser Val		Gly					Glu					Ala			4 608
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20	cgg gtg Arg Val					Lys					Met					4704
25	gac aca Asp Thr 1570				Ala					Gly						4752
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	ccc tgc	ccc	tgc ·	cec :	:gc	೦೦೦	tgt	gat	ggc	ccg	agg	ctg	೦೦೦	act	agt	5232

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	Lys Met Ala	
40	•	

INTERNATIONAL SEARCH REPORT

Intern Ial Application No PCT/US 98/23161

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C12N15/12 C07K CO7K14/705 C07K16/28 C12N5/10 G01N33/68 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category ' Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. WO 95 04144 A (NEUREX CORP) X 1,2,7, 9 February 1995 10-1820-22 Y see abstract; claims 1-10 3,19 X NOONEY JM (REPRINT) ET AL: "Identifying 1,2, neuronal non-L Ca2+ channels - more than 10-16. stamp collecting?" 20-22 TRENDS IN PHARMACOLOGICAL SCIENCES. 10-1997, 18, 363-371, XP002093637 see page 369, right-hand column - page 370, right-hand column X Further documents are listed in the continuation of box C. X Patent family members are listed in annex. * Special categories of cited documents: *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the lart which is not considered to be of particular relevance invention earlier document but published on or after the international "X" document of particular relevance; the claimed invention filing date cannot be considered novel or cannot be considered to document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the "O" document reterring to an oral disclosure, use, exhibition or document is combined with one or more other such docu-ments, such combination being obvious to a person skilled in the art. other means document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 16 February 1999 09/03/1999 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Gurdjian, D Fax: (+31-70) 340-3016

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Intern Ial Application No PCT/US 98/23161

C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	PCT/US 98/23161
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
х	ERTEL S I ET AL: "Low-voltage-activated T-type Cachannels" TRENDS IN PHARMACOLOGICAL SCIENCES, vol. 18, no. 2, February 1997, page 37-42 XP004055849 see page 39, left-hand column, paragraph 4 page 40, middle column, paragraph 1; table 1	1,2, 10-16, 20-22
X	DZHURA IO ET AL: "Characterization of hypothalamic low-voltage-activated Ca channels based on their functional expression in Xenopus oocytes." NEUROSCIENCE, FEB 1996, 70 (3) P729-38, XP002093638 UNITED STATES see the whole document	1,2, 10-18, 20-22
Y	WILSON R ET AL: "2.2 MB OF CONTIGUOUS NUCLEOTIDE SEQUENCE FROM CHROMOSOME III OF C ELEGANS" NATURE, vol. 368, 3 March 1994, pages 32-38, XP002910426	3,19
Y	see abstract & EMBL DATABASE Accession number q18840 WILSON R. ET AL. 1996 see the whole document	3,19
A	WO 93 04083 A (SALK INST BIOTECH IND) 4 March 1993 see abstract; claims 1-39	1-22
P,X	PEREZ-REYES E ET AL: "Molecular characterization of a neuronal low-voltage-activated T-type calcium channel 'see comments!" NATURE, FEB 26 1998, 391 (6670) P896-900, XP002093639 ENGLAND see the whole document	1-15, 20-22
Ρ, Χ	CRIBBS LL ET AL: "Cloning and characterization of alphalH from human heart, a member of the T-type Ca2+ channel gene family." CIRC RES, JUL 13 1998, 83 (1) P103-9, XP002093640 UNITED STATES see the whole document	1-22

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